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Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, susceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

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FRONT COVER: NAVAL MEDICAL RESEARCH UNIT NUMBER TWO. This research activity was first established in 1942 at the Rockefeller Institute in New York City to study tropical diseases affecting American troops stationed in the South Pacific. By 1945 NAMRU-2 was operating as a wide ranging field research unit with headquarters on Guam. Although deactivated at the war's end, it was reinstated in Taipei, Taiwan, on 30 September 1955 and recommissioned on 7 November 1957. Since then it has conducted studies of infectious and tropical diseases and other health problems, not only in Taiwan, but in the whole Western Pacific and Southeast Asia area. It has managed to bring under control many an outbreak of diseases such as scrub typhus, filariasis, and certain types of dysentery. While primarily concerned with diseases of potential military significance the Unit has gained its scientific reputation by achievements in the fields of cholera, trachoma, and virus and parasitic diseases that occur among the native populations. Since 1958 methods for treating cholera have been so improved that the mortality rate has fallen from 60 percent to less than 1 percent in uncomplicated cases and to 3 percent in cases associated with heart disease or tuberculosis. In 1957 the Unit isolated the virus which causes trachoma, a blinding disease which infects the eye tissues of millions, and is now working on a vaccine which will provide immunity from it. The life cycles and modes of transmission of parasitic diseases have been studied with a view to discovering preventive methods, and ways of rapidly and accurately identifying these diseases have been developed and evaluated. NAMRU-2 has also supplied diseased specimens for laboratories throughout the world. Most recently, in February 1967 it opened a medical and surgical research center in tropical medicine at the Naval Support Activity Hospital in DaNang, Vietnam. This center is studying insect-borne, diarrheal and parasitic diseases, evaluating the effects of heat stress on field troops, and investigating tropical fevers and poisonous snakes. It is cooperating with other research activities in advanced studies of shock treatment in combat casualties.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

COMPARISON OF THE MICROCIRCULATORY AND THE CENTRAL HEMATOCRIT AS A MEASURE OF CIRCULATORY SHOCK

Donald B. Doty, MD, and Max Harry Weil, MD, Los Angeles, California,
Surg Gynec Obstet 124(6):1263–1266, June 1967.

The hematocrit, or packed cell volume, is a simple and reliable in vitro measure of the partition between red cells and plasma in a specimen of blood. In the microcirculation, the proportion of red blood cells and plasma is actually determined by the size of the vessels and the rate of blood flow through them. During shock, when blood flow is reduced and small arteries and veins are markedly constricted, the concentration of red cells within the vessels increases. The possibility that this selective increase in hematocrit of blood sampled from the microcirculation might serve as an objective measure of the severity of circulatory shock in patients is the subject of the present study.

Method

The microhematocrit was determined in duplicate samples of blood obtained from three sites which were an indwelling catheter placed by the percutaneous Seldinger technique in the brachial or femoral artery, a polyethylene catheter advanced through surgical cutdowns of the basilic vein into the superior vena cava or right atrium, and puncture of the finger pad of the third or fourth digit using a No. 18 gauge sterile needle or a disposable lancet to establish spontaneous flow of blood from the microcircuit. Because we were unsuccessful in our attempts to withdraw blood from peripheral veins during shock in 19 out of 22 patients examined, initial attempts to correlate the peripheral venous hematocrit with the microcirculatory hematocrit were abandoned.

The blood was collected in dry heparinized capillary tubes 75 millimeters long and 1.4 to 1.6 millimeters in diameter. The tubes containing the blood samples were sealed and centrifuged for a period of five minutes in a microhematocrit centrifuge. A microcapillary reader was used to measure the column of packed cells. Duplicate microhematocrit readings were obtained from each site. Pairs of measurements which failed to agree with one percent were discarded. In each such instance, additional samples were taken for analysis until this requirement was satisfied. Intra-arterial pressure was measured with a strain gauge manometer and recorded on a direct writing multichannel recorder.

Cardiac output was determined by the dye dilution technique, with the injection of indocyanine green into the central venous catheter. A photoelectric densitometer was used, and recordings were made. The recorded dye curves were analyzed either directly or off-line, with the aid of computer techniques for the measurement of cardiac output, appearance time, and mean circulation time according to methods previously described by Rockwell and his associates. Serum lactic and pyruvic acid levels were measured by the method of Marbach and his co-workers as an index of the metabolic disturbance that followed the critical reduction in tissue perfusion which is characteristic of shock. An indwelling urethral catheter was used for the collection of urine. Urine output was recorded on an hourly basis. The complete analytic procedure was accomplished on a total of 92 occasions with 40 consecutive patients.

The patients were divided into two groups, shock and nonshock. Twenty-five observations were made in 18 patients who exhibited the classic physical signs of shock. The subjects were unselected with regard to the cause of shock. Shock was related to hypovolemia in six patients, myocardial injury in two, bacterial infection in five, and neurologic injury in two. In each patient, a marked reduction in arterial blood pressure, a definitive reduction in cardiac output, and a critical decrease in urine flow were documented. For purposes of comparison, the nonshock group included 67 observations on 22 patients who were critically ill but not in a state of shock and some of the 18 patients in whom shock

From the Shock Research Unit and the Departments of Surgery and Medicine, University of Southern California School of Medicine, and the Los Angeles County General Hospital, Los Angeles.
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had been reversed. The nonshock group in no way represents an idealized control group; however, there were distinct differences in the objective measurements (Table 1).

TABLE I.—CIRCULATORY MEASUREMENTS OF PATIENTS, MEAN VALUES

	—Observations— Shock	Nonshock	Normal values, mean
No. of observations	25	67	
Mean arterial pressure, mm. Hg	60	79	87
Cardiac index, L./min./M²	1.82	3.78	3.20
Mean circulation time, secs	27.8	17.5	12.8
Lactic acid, mM./L.	6.08	3.61	<1.0

Results and Discussion

Simultaneous arterial and central venous hematocrit values were identical in 88 out of 92 determinations. Since the correlation coefficient between these two measurements was 0.99, the arterial and central venous hematocrits were considered to be the same and were referred to as the central hematocrit.

The hematocrit obtained from the finger pad is commonly referred to as the capillary hematocrit. Since the blood is actually from small arterial and venous vessels, this term is not entirely valid. However, in adopting current convention, we use the terms microcirculatory hematocrit and capillary hematocrit interchangeably.

The capillary hematocrit differed from the central hematocrit in 70 of the 92 determinations. It was as much as three volumes percent less and as much as 10 volumes percent greater than the central hematocrit. The greatest differences were observed in the patients with circulatory shock. For convenience, the algebraic difference between the capillary and central hematocrits was referred to as the hematocrit gradient.

The distribution of hematocrit gradients is shown in Figure 1. In the nonshock group, the mean hematocrit gradient was −0.1 volume percent. In the shock group, however, the mean hematocrit gradient was +2.1 volumes percent. The differences between these groups were highly significant, $p < 0.0001$.

The hematocrit gradient was then evaluated in terms of the severity of the circulatory disorder. For statistical analysis, an index was established based on a gradation from zero to four units. One unit was assigned to each of the following hemodynamic abnormalities: a mean arterial pressure of less than 70 millimeters of mercury, a cardiac index of less than two liters per minute per square meter, an appearance time of indocyanine green greater than 10 seconds, and a mean circulation time greater than 20 seconds.

A score of zero indicated circulatory competence and a score of four was obtained in patients with advanced shock in whom cardiac output and arterial pressure were reduced, and the velocity of blood flow was characteristically prolonged. A linear relationship was noted between the severity of the circulatory disorder and the frequency with which positive hematocrit gradients were observed.

Duplicate microhematocrit determinations in clinical laboratories generally vary from one to three volumes percent. Because of this variability which is primarily due to variations in sampling technique and visual errors in measurement, only hematocrit gradients of three or more volumes percent were considered significant. The variability of duplicate measurements of the microhematocrit in our laboratory actually did not exceed one volume percent, an indication of the conservative implication of this decision.

A significant hematocrit gradient of three or more volumes percent was observed in 13 of the 40 patients. In 10 of these patients, circulatory shock was clearly present. The other three were critically ill but did not fulfill all of the criteria for shock. Three false-positive hematocrit gradients were observed among 67 measurements in the non-shock group of patients. There was additional objective evidence of perfusion failure in these three patients, however. Lacticacidemia was detected in two of these patients and renal failure in a third.

Comment

Under normal conditions, the hematocrit of blood obtained from the finger pad is the same as, or slightly less than, that obtained from a peripheral vein. Similarly, in patients as in experimental animals, the capillary hematocrit is normally the same as, or less than, the hematocrit obtained from central locations. In a study reported by Polosa and Hamilton, the average red cell concentration of blood obtained from the paw of the normal dog was two percent less than that of blood obtained from the superior vena cava. In this study which included critically ill patients, the capillary hematocrit was usually the same as, or slightly lower than the central hematocrit except for the patients who were in a state of shock.

During circulatory shock, however, a relative increase was demonstrated in the capillary hematocrit. This increase in the hematocrit from the

finger pad reflected the changes which would be predicted from studies of the microcirculation during shock. Chambers and his colleagues studied the microcirculation in rats subjected to trauma. Close packing of red blood cells and hemoconcentration were observed in the capillary circulation of the mesoappendix. In monkeys, Knisely and his associates described conglomeration of red cells after trauma that formed a thick, mucklike sludge, the source of the term sludging. Shoemaker and his associates showed that cellular aggregation also occurred in the hepatic sinusoids and in postcapillary venules of the peripheral circuit in animals during hemorrhagic shock. Hardaway and his coworkers implicated decreased capillary perfusion with cellular aggregation and disseminated intravascular coagulation in the pathogenesis of irreversible shock. By 1964, Knisely and his associates found intravascular aggregation of blood cells in 195 human beings with trauma, fractures, and shock.

The alterations in the capillary hematocrit may also be due to venular constriction related to shock. Hypotension is, in part, compensated by the constriction of precapillary arteriolar sphincters. However, the constriction of venular sphincters may even be more important in the present context, since the constriction of these vessels results in blockage of capillary outflow. This situation, in turn, increases hydrostatic pressure within the capillary vessels. Fluid leaks from the vascular space because hydrostatic pressure in the capillaries proximal to the constricted venules now exceeds the colloid osmotic pressure. The consequent reduction in the plasma volume without change in the red cell concentration is a probable cause of the relative increase in capillary hematocrit observed during shock.

At the bedside, diagnosis of shock is based on the clinical appearance of the patient which includes decreased mentation, cold moist skin, peripheral cyanosis, a fall in blood pressure, and a reduction in urine flow. These signs may not be individually reliable indicators of circulatory failure, but the objective demonstration that effective blood flow and tissue perfusion are reduced is fundamental to the clinical diagnosis of shock. The relative elevation of the capillary hematocrit when compared to the central hematocrit, considered together with the clinical signs, is an additional diagnostic aid and has the added advantage of objective quantitation of severity.

Summary

Measurement of the microhematocrit on samples of blood obtained simultaneously from the fingertip and the central venous catheter, or from an artery, provided an indication of the extent to which peripheral blood flow was reduced. The algebraic difference between the central venous and the capillary hematocrits was defined as the hematocrit gradient. Increases in this gradient to levels of three volume percent or more were observed in a majority of patients during shock. This gradient also served as a quantitative index of the severity of circulatory shock.

This bedside test is attractively simple, requires no special equipment or personnel, and is easily repeated at frequent intervals. Its reliability as an indicator of shock compares favorably with the more complicated hemodynamic and metabolic measurements. Viewed as an adjunct to clinical evaluation and as an objective guide to treatment, the test is a useful measurement at the bedside of the patient in a state of shock.

(The omitted figures and references may be seen in the original article.)

THE NEW VACCINES

Harry M. Meyer, Jr., MD, National Institutes of Health, Bethesda, Maryland,

Postgrad Med 42(6):453–456, December 1967.

New vaccines being developed offer excellent prospects for control of several important diseases. A live attenuated mumps virus vaccine is expected before the end of 1967, and a rubella vaccine within the next few years. Clinical trials are being conducted with vaccines of killed-virus and live-virus materials for the prevention of respiratory diseases.

Since the time of Edward Jenner we have used vaccines to control viral diseases. During the past decade the technologic advances attending the propa-

gation of viruses in tissue cultures have led to the development of several new vaccines. Vaccines currently being developed hold promise of preventing still other diseases.

Specific in action, viral vaccines evoke a protective antibody response in recipients. Inactivated vaccines are prepared by chemically or physically "killing" the virus without destroying its immunogenicity. The "live"-type vaccines make use of attenuated strains of the agent. Here the virus should have little or no pathogenicity for man but must retain the ability to infect and thereby induce an immune response.

Numerous technical problems make unlikely the possibility of developing a vaccine for every viral disease. Recognition of the viral etiology of a particular disease does not constitute the start of vaccine development. For example, measles and rubella were known to be caused by viruses long before the critical first step could be taken. Isolation and propagation of the agent in a suitable laboratory host signal the beginning. For the live vaccines the virus must then be manipulated during successive growth cycles so that less pathogenic variants can be recognized and selected if and when they emerge. For each of our modern live-virus vaccines this was a time-consuming process.

To prepare a successful inactivated vaccine requires a considerable concentration of the virus or its antigenic material, since increase in antigenic mass as a result of replication of the agent does not occur in the vaccinee to assist in immunologic stimulation. In many instances our best production technics are not good enough to produce the virus in adequate quantity. For this same reason the killed agent must be relatively antigenic; experience has shown that some viruses are better than others in this respect.

Regardless of the efficiency of a vaccine in stimulating antibodies, it will be protective only if the immunologic character of the disease-causing virus remains constant. Influenza viruses are notorious for their frequent shifts in antigenic components; thus, a good vaccine for yesterday's virus may offer little protection against tomorrow's epidemic.

Unfortunately, many viruses may be stable in immunologic characteristics but exist in multiple antigenic types, each capable of producing disease. For example, there are more than 30 immunologically distinct types of Coxsackie viruses. A similar situation prevails with many respiratory agents, e.g., the rhinoviruses and adenoviruses. Here, development of potent monovalent vaccines may be technically feasible, yet the prospects for effective disease prevention are discouraging because of the multiplicity of vaccines and inoculations that would be necessary for complete immunization. Single types of viruses may cause measles, mumps, rubella and varicella, while only three serotypes cause poliomyelitis, making protection by vaccines feasible.

A final feature concerns the pathogenesis of the disease in question. In poliomyelitis, measles, mumps, rubella, varicella and many other diseases, symptoms appear only after a rather long incubation period. Exposure and initial replication of the agent in the susceptible cells of the respiratory or intestinal tract do not lead to disease. Illness occurs only after considerable spread of the virus, usually through one or more viremic phases, to specific target organs. In infections of this type even minimal levels of circulating vaccine-induced antibodies can be fully protective. By contrast, in many respiratory diseases long incubation periods and systemic dissemination of virus are not necessary. The virus multiplies locally in the respiratory tract and promptly produces symptoms. In this instance circulating antibodies are much less important, and effective immunity probably depends more on levels of immune substances in the respiratory tract secretions. Under these circumstances even vaccines of apparently high antigenicity may not give effective protection.

Despite these problems new vaccines presently or soon to be available offer excellent prospects for the control of several important diseases. In recent years the widespread use of the poliovirus vaccines has virtually eliminated poliomyelitis from the United States and several other nations. Measles vaccines, which first became commercially available only five years ago, are similarly used extensively in a national program aimed at eradicating measles. Incredible as it seems the coming generation of physicians may never know these and other formerly common maladies, just as most of us have not dealt with smallpox.

A considerable research effort is underway in the field of respiratory virus vaccines. Unfortunately, here we are plagued by the antigenic shifting of the influenza viruses and the diversity of immunologic types of other viruses capable of causing respiratory disease. The licensed inactivated influenza and adenovirus vaccines are well known to physicians. Killed-type preparations of parainfluenza and respiratory syncytial viruses are being tested experi-

mentally. Clinical tests have also been made with live influenza, adenovirus type 4, respiratory syncytial and rhinovirus materials. Investigations with the live adenovirus type 4 strain are perhaps the most advanced. The experimental vaccine is administered orally in capsule form, does not produce undesirable reactions, and gives significant protection. Use of such a vaccine would probably be limited since epidemic disease caused by adenovirus type 4 has been shown to occur only in military recruits and perhaps other special groups housed under dormitory-type conditions. The inactivated parainfluenza material appears promising and would have a wider application since the parainfluenza viruses have been shown to be important respiratory pathogens in children.

A live attenuated mumps virus vaccine is expected to become available in late 1967. Similar in many respects to the technic used in the development of measles vaccine, the virus was attenuated by passage in chick embryo tissue cultures. The mumps vaccine, unlike the live-virus measles vaccines, does not produce any recognizable reaction in recipients, but it, too, appears to confer a solid immunity after a single injection. Like other attenuated viruses, the Jeryl Lynn mumps strain evokes somewhat lower levels of antibodies than the natural disease. For this reason long-term surveillance of the immunity status of the first groups experimentally inoculated is extremely important. Presently, these follow-ups extend over a two year period and have shown a continued immunity and stable levels of antibody.

The rubella epidemic of 1963 to 1965 is still very much in our minds. Since rubella virus exists as a single immunologic entity and requires a long incubation period, the disease should be readily preventable by vaccination. Attenuated strains of the virus developed during the past two years are currently under clinical trial here and abroad. From the experimental data collected thus far, it appears that the attenuated virus possesses those characteristics essential to its use as a vaccine. Inoculated volunteers have remained asymptomatic but have developed antibodies with regularity. These antibodies have persisted for two years with little change. Moreover, several vaccinees challenged with natural rubella virus a year after their original inoculation were fully protected. It seems reasonable to expect a rubella vaccine to become available in the next few years, well in advance of our next expected epidemic.

Mention of smallpox vaccine seems inappropriate in a discussion of new vaccines, yet this is not the case. In past years when smallpox occurred in the United States, our chief concern was to insure the general availability of potent vaccine. The local and systemic reactions commonly accompanying primary immunization and even the infrequent but severe complications were accepted as a matter of necessity. Today, several groups here and abroad are working to develop more attenuated strains of vaccinia virus or inactivated materials that might be used with greater safety. Habits are notoriously hard to change and vaccination customs are no exception. We should critically appraise these new approaches to smallpox immunization; superior methods may become available.

In the coming years we may have the opportunity to employ live vaccines not only for smallpox, yellow fever, poliomyelitis and measles, but also for mumps, rubella, varicella and several respiratory viral diseases. With such a potential it may become important to use new techniques in administering vaccines. As pointed out earlier, with either live-virus or killed-virus vaccines, the ultimate problem is having to give many separate injections in order to protect the individual against all the agents for which effective vaccines might be produced. The use of combined vaccines may represent an attractive alternative. Indeed, the three monovalent live polioviruses are often given in combination, and in many areas overseas smallpox and yellow fever vaccines have been given together for over 25 years.

Combinations offer no immunologic advantage but might permit physicians to complete the immunization of larger numbers of persons than could be reached if numerous return visits were necessary. Perhaps this would be especially appropriate if the disease in question had been eradicated but there remained a need to maintain a reasonable level of herd immunity. A combined measles-smallpox vaccine has been tested experimentally and should become available in the near future. It seems likely that other combined products may also be developed.

Vaccines are not destined to resolve all of our problems with the viruses. However, new vaccines will permit control or eradication of several major diseases formerly unassailable.

ACCURACY OF THE CLINICAL DIAGNOSIS OF PULMONARY EMBOLISM

Frank J. Hildner MD, and Robert S. Ormond MD,
JAMA 202(7):567–570, Nov 13, 1967.

The accuracy of the clinical diagnosis of pulmonary embolism was evaluated in 78 patients. The clinical diagnosis of a pulmonary embolus derived from history, symptoms, physical findings, electrocardiogram, laboratory enzymes, roentgenogram of the chest, and isotope lung scan was compared to that established by pulmonary angiography. Pulmonary emboli were demonstrated in only 32 (41 percent) of the 78 patients studied. Reasons for illness in the 46 (59 percent) patients without emboli were chiefly atelectasis, congestive heart-failure, and pneumonitis. Except for phlebitis, no element of the history clearly favored or opposed emboli. Neither symptoms, physical findings, ECG, serum enzymes, nor chest roentgenography were able to distinguish patients with embolism. The isotope lung scan could accurately detect defects in lung perfusion but was unable to differentiate causes. Pulmonary angiography remains the most objective and definitive diagnostic method.

Pulmonary embolism may no longer be primarily a medical disease to be diagnosed at the bedside. The degree of embolism does not necessarily correspond to clinical symptoms or findings, and the presence of the disease is frequently unsuspected. Conversely, the erroneous diagnosis of pulmonary embolism may be more frequent than many clinicians wish to believe.

Whenever pulmonary embolism is diagnosed, a decision to treat it medically or surgically must be made. Medical treatment of a massive embolism may be inadequate, and surgical treatment of a serious disease such as congestive heart-failure masquerading as pulmonary embolism may have a tragic result. Thus any decision regarding the treatment of this disease necessarily depends on an accurate and speedy diagnosis.

From the Adult Physiology Laboratory, Division of Cardiovascular Diseases (Dr. Hildner), and the Division of Diagnostic Radiology, Department of Radiology (Dr. Ormond), Henry Ford Hospital, Detroit. Dr. Hildner is now with the Mount Sinai Hospital, Miami Beach, Fla.

Reprint requests to 4300 Alton Rd, Miami Beach, Fla 33140 (Dr. Hildner).

For these reasons, an evaluation of the accuracy of the clinical diagnosis of pulmonary embolism was undertaken. The courses of illness in patients who had had pulmonary angiography performed for suspected pulmonary embolism were reviewed in detail. An analysis of the ability of history, symptoms, physical findings, electrocardiogram, laboratory enzymes, roentgenogram of the chest, and isotope lung scan to establish the diagnosis of pulmonary embolism as compared to the findings of pulmonary angiography is presented.

Material

Seventy-eight hospitalized patients in whom pulmonary embolism was diagnosed clinically were referred to the cardiac physiology laboratory for catheterization of the right side of the heart and pulmonary angiography. These patients were drawn from both medical and surgical services and varied widely in degree of illness. Some had only minimal symptoms, whereas others were moribund. Since the clinical diagnosis of pulmonary embolism had already been made in each case, objective evaluation by isotope lung scan and pulmonary angiography was made to determine degree of involvement. Many other hospitalized patients with a similar clinical diagnosis and course were not available for objective study by either method. These suspected but unconfirmed cases are excluded from this series. All patients referred for angiography were studied, and case selection was not attempted. In those patients demonstrating acute onset of symptoms (55 or 70 percent), angiography was completed within 24 hours. In the remaining patients in whom symptoms occurred insidiously (23 or 30 percent), angiography was performed within five days.

Methods

An analysis was done of the sequence of clinical events leading to angiography. In each case, the history of illness was reviewed, and the major diagnosis or diagnoses were determined. The patient's

symptoms and physical findings recorded in the pre-catheterization evaluation were summarized. Where possible, the ECG, serum enzyme determinations, chest roentgenogram, and lung scan, which were used to make the clinical diagnosis of embolism, were tabulated.

Technique of Angiography.—Pulmonary angiography was performed with the patient in the anteroposterior projection. The largest catheter that could be conveniently inserted was positioned in the main pulmonary artery, and 75 percent diatrizoate sodium (Hypaque) and meglumine warmed to 45 C was injected as rapidly as possible. Large sequential chest x-ray films were obtained rapidly, until the pulmonary arteries were cleared and the pulmonary veins were filled. In patients with a normal roentgenogram of the chest and, at most, minimal elevation of pulmonary artery pressure, a run of seven seconds was usually sufficient. If the pulmonary artery pressure was moderately elevated or if there were infiltrative or atelectatic changes in the lungs, the duration of filming was prolonged to assure complete opacification of the vascular tree. In exceptional cases, flow of contrast medium through atelectatic but otherwise intact segments may have been prolonged beyond 20 seconds. In cases such as these, the vessels within these segments may have appeared obstructed in any particular frame; therefore, filming was continued until the terminal vessels were opacified. If the filming were prematurely terminated, such a case would have been mistakenly interpreted as having an occluded vessel.

Interpretation of Angiography.—To insure accurate diagnosis, angiography should be performed early in the course of the illness prior to absorption, retraction, or fragmentation of the emboli. Emboli produce filling defects of varying degrees of obstruction within the lumena of the vessels. Complete occlusion of a large vessel is the exception. Some contrast usually can be seen oozing beyond the site of obstruction. The defects tend to be irregular and elongated. They lodge at the divisions of vessels, producing globular and stringy lucencies in the primary vessel, and extend into the divisions. The filling defect may measure centimeters in length. There is a reduction in number of small vessels filled as well as a reduction in the opacification of the segments of lung supplied by the involved artery. The flow in the affected segment is retarded with a reduced or absent parenchymal blush.

Individual vessels as small as 1 mm in diameter can be distinguished on a normal pulmonary angiogram in which the vascular bed is seen as uniform throughout. In such a patient, the occlusion of a vessel as small as 2 to 3 mm can be readily appreciated. However, the majority of patients do not present such a picture. Many patients have pulmonary congestion, pulmonary infiltration, basilar atelectasis, pleural effusion, or combinations of such processes. In these patients, the vascular bed is not homogeneous and blood flow is not uniform. Some segments have normal perfusion, while in others the vessels are crowded and flow is retarded. Recognition of an occluded vessel beyond the third generation (subsegmental) is difficult.

Results

Pulmonary emboli were demonstrated in 32 or 41 percent (positive) of the 78 patients studied. There was no evidence of emboli in the remaining 46 patients (59 percent, negative). Table 1 lists the diagnosis established after angiography in the negative cases. Atelectasis, congestive heart-failure, and lung infections were most often found to be responsible for these patients' illnesses. In five cases, no disease process could be established. Review of each of the 78 cases six months after angiography did not appreciably change earlier diagnoses.

TABLE 1.—Final Diagnosis in 46 of 78 Patients With Suspected Pulmonary Embolism

Diagnosis	*No. of Patients*
Atelectasis	13
Congestive heart-failure	11
Pneumonitis	9
No obvious disease	5
Primary pulmonary hypertension	2
Anomaly of lung	2
Myocardial infarction	1
Bronchitis	1
Pneumothorax	1
Pulmonary hypertension, mitral stenosis	1

History.—Historical events that could cause or predispose to emboli were sought in each case. In addition, any other disease process that contributed significantly to the clinical state of each patient was noted (Table 2). A history of previous phlebitis and malignancy was found more often in the positive cases. Congestive heart-failure and existing venous disease occurred more often in cases with negative results. Recent surgery and a history of previous emboli, use of oral contraceptives, bed rest over five days, pneumonitis, trauma (including bone fractures and contusions), the postpartum state, cerebrovascular accident, asthma, or pancreatitis were not helpful in making a diagnosis. Except for previous phlebitis, no element of the history clearly favored or opposed a diagnosis of embolism.

Table 2.—Suspected Pulmonary Embolism in 78 Patients

History	Emboli Present: No. of Patients	Emboli Present: % of 32 Patients	Emboli Absent: No. of Patients	Emboli Absent: % of 46 Patients
Previous phlebitis	11	34	5	11
Malignancy	7	21	5	11
Congestive heart-failure	3	8	12	26
Venous disease	0	0	6	13
Recent surgery	6	19	10	22
Previous emboli	5	16	9	20
Oral contraceptives	1	3	3	7
Prolonged bed rest	6	19	5	11
Pneumonitis	3	9	2	4
Trauma	4	12	3	7
Postpartum state	0	0	1	2
Cerebrovascular accident	1	3	0	0
Asthma	0	0	1	2
Pancreatitis	0	0	1	2
Symptoms				
Acute onset	24	75	30	65
Insidious onset	8	25	16	35
Chest pain	17	53	26	57
Other pain	5	16	8	17
No pain	9	28	13	28
Hemoptysis	11	34	10	22
Shock	5	16	3	7
Cough	2	6	7	15
Dyspnea	10	32	16	35
Physical Findings				
Heart rate				
Under 100 beats per minute	19	60	29	63
Over 100 beats per minute	13	40	17	37
Cardiac rhythm				
Regular sinus	27	84	34	74
Atrial fibrillation	5	16	12	26
P_2 accentuated	7	21	13	28
Pleural friction rub	2	6	3	7
Leg varicosities	6	19	10	22
Blood pressure (under 100/70 mm Hg)	8	25	4	8
Diaphoresis	7	21	5	11
Ventricular diastolic gallop	4	12	2	4
Pulmonary rales	17	53	17	37
Peripheral phlebitis	8	25	6	13
Leg tenderness	12	38	9	20
Leg swelling	10	32	12	26
Pulmonary impairments	9	28	25	54
Fever	2	6	11	24
Cyanosis	0	0	1	2
Serum Enzymes				
Normal	13	40	15	33
SGOT elevation	6	19	7	15
Serum lactic dehydrogenase elevation	7	21	12	26
No study	9	28	14	31
Electrocardiogram				
Normal	23	72	40	87
Right bundle-branch heart-block	3	9	5	11
Right ventricular hypertrophy	1	3	3	7
Inverted T wave, leads V_1-V_3	3	9	2	4
S-I, Q-III, T-III	6	19	4	8
Roentgenograms of the Chest				
Normal	1	3	9	20
Congestive heart-failure	3	9	9	20
Pleural fluid	7	21	8	17
Atelectasis	5	16	10	22
Infiltrate	22	69	19	41
Pneumonia	1	3	3	7
No study	4	12	1	2

Symptoms.—There were no symptoms which distinguished patients with emboli from those without. Acute or insidious (more than 24 hours) onset of symptoms occurred equally in patients with and without emboli and therefore was not helpful in making a diagnosis. The presence or absence of pain, including pleuritic, nonpleuritic, shoulder, abdominal, or any other, occurred equally in both groups. Hemoptysis and shock (sudden vascular collapse) were found slightly more often in patients with emboli. Cough was seen more in nonembolism. Dyspnea (with the patients at rest) occurred equally in both groups. The symptoms of chest pain, hemoptysis, dyspnea, and cough, even if combined, did not distinguish cases with emboli.

Physical Findings.—Tachycardia or bradycardia, a regular or irregular cardiac rhythm, accentuated pulmonic second sound (P_2), pleural friction rub, and leg varicosities were found equally in patients with and without emboli. The findings of a blood pressure below 100/70 mm Hg, diaphoresis, ventricular diastolic gallop sound, pulmonary rales, active phlebitis, leg tenderness, and edema favored the presence of an embolus somewhat; whereas, fever and impairment of pulmonary breath sounds or percussion note were more frequent in patients without emboli. Although no single portion of the physical examination was clearly helpful in designating the patients with emboli, these data indicate that a shock-like syndrome favors the presence of emboli.

ECG.—The ECG was normal in 23 (72 percent) of the patients with emboli and in 41 (89 percent) of those without. The presence of right bundle-branch heart-block or right ventricular hypertrophy did not favor either alternative. Inversion of the T wave across the right precordium and a S-I, Q-III, T-III pattern were found somewhat more frequently in the patients with emboli.

Enzymes.—Evaluation of serum glutamic oxalacetic transaminase (SGOT) and serum lactic dehydrogenase (LDH) tests was not available in every case. In those patients having these studies, the SGOT and LDH levels were elevated with equal frequency in both groups. Strangely, normal enzyme levels were found slightly more frequently in emboli cases.

Roentgenogram.—A normal roentgenogram of the chest was found far more frequently in patients without embolism. The presence of congestive heart-failure also favored the absence of emboli somewhat. The findings of atelectasis, pulmonary infiltrates, pleural fluid, and pneumonia on chest

x-ray films occurred with about equal frequency in the two groups of patients. No feature of routine roentgenograms of the chest was clearly helpful in diagnosing or excluding embolism.

Syndromes.—The triad of chest pain, hemoptysis, and peripheral venous disease was present in 4(13 percent) emboli and 5(11 percent) nonemboli cases. The addition of pulmonary infiltrates demonstrated by roentgenography, and an accentuated P_2, does not change the incidence of occurrence in either group.

Isotope Lung Scan.—Isotope lung scans with the use of iodinated I 131 serum albumin aggregated were performed on 17 patients before angiography. In seven patients, lung scans demonstrated perfusion defects which were confirmed to be emboli by angiography. In four cases, both lung scan and angiogram failed to show any vascular obstruction. In the remaining six patients, the lung scan demonstrated perfusion defects, that were shown by angiography to be due to pneumonia in two patients, congestive heart-failure in two, atelectasis in one, and chronic pulmonary scarring in one. The isotope lung scan accurately designated the areas of absent or reduced perfusion of the lung but was not diagnostic of the cause.

Comment

Originally, this study was an attempt to derive a typical pattern of illness from the case histories of patients with pulmonary emboli. Since some objective measure of embolism was needed to form a uniform basis for comparison, those patients undergoing pulmonary angiography prior to anticoagulation therapy or possible embolectomy were the best choice. Within a very short time it became clear that many of the patients so studied did not have embolic disease and that there was actually a poor correlation between the clinical diagnosis of pulmonary embolism and that established by angiography.

The results of this study are unconventional but very striking. They strongly suggest that our old ideas concerning pulmonary embolism and our current diagnostic techniques, short of angiography, need radical revision. It is possible, of course, that the patient material used is not representative of the usual cases diagnosed as pulmonary emboli. Such an objection suffers from the fact that the "usual" cases are not subjected to objective diagnostic tests and therefore offer a poor group for comparison. It is also possible that the large error of clinical diagnosis was due to a great overlap of nonspecific historical elements. Symptoms, and findings caused by nonembolic disease. This is obviously true and clearly demonstrates that in complicated cases, where diagnoses such as congestive heart-failure, pneumonia, and the postoperative state occur, the more symptomatic the patient, the more insecure is any diagnosis of embolism.

Pulmonary embolism has been reported to be the most common lung condition found in a general hospital population with perhaps 80 percent to 90 percent of embolic episodes going unrecognized. The explanation for this situation becomes obvious when it can be shown that clinical and laboratory criteria, time honored as diagnostic of pulmonary embolism, are unreliable. The classic triad of phlebitis, hemoptysis, and chest pain suggests infarction. This same triad, however, may be present in suspected cases shown to be free of emboli. Furthermore, no clinical observation, with the exception of the history or the actual presence of phlebitis, offers diagnostic accuracy. The ECG often fails to help, probably because the characteristic changes do not occur or are evanescent. The judicious use of enzymes, especially LDH and SGOT, may be helpful but is not specific. The plain x-ray film of the chest in cases of suspected pulmonary emboli is helpful mostly in excluding pulmonary disease.

An attempt should be made to document the presence or absence of emboli in suspected cases where a predisposing condition exists. This search is justified especially in critically ill patients in whom pulmonary embolectomy or prevention of a massive fatal embolus by vena caval interruption could be lifesaving. The evidence presented here demonstrates that these decisions cannot be based on bedside evaluation or elementary laboratory tests. The accurate diagnosis of pulmonary embolism requires the use of all available diagnostic methods. At the present time the radioisotope lung scan is an accurate screening guide to defects in lung perfusion; but it is not specific in differentiating causes of any reduced flow. Therefore, although subject to limitations in interpretation and performance, pulmonary angiography remains the clinician's most objective and definitive diagnostic method.

Generic and Trade Names of Drugs

Diatrizoate sodium—*Hypaque.*

Diatrizoate meglumine—*Cardiografin, Gastrografin, Renografin.*

Iodinated I 131 serum albumin aggregated—*Human Aggregated Radioiodinated I 131 Albumin, Human MAA 131, Albumotope-LS.*

(The references may be seen in the original article.)

MEDICAL USES OF THE WOOD'S LAMP

Richard M. Caplan, MD, JAMA 202(11):1035–1308, Dec. 11, 1967.

A Wood's lamp is a source of ultraviolet radiation of wavelengths centered around 3,650 Angstrom units, and ranging from approximately 3,200 A to 4,000 A. It thus excludes most of the burning and tanning rays shorter than 3,200 A and the visible light rays longer than 4,000 A. This portion of the electromagnetic spectrum is also called long-wave ultraviolet, near ultraviolet, or blacklight.

For many years it has been known that near ultraviolet will excite fluorescence of a great many substances, a fact much exploited in advertising, industry, and general scientific investigations. Physicians and medical investigators have also used this type of energy to help understand some of the biologic processes that concern them. Such uses are the subject of this paper.

Although one may employ complicated and powerful equipment plus precise and expensive filters to obtain greater precision of wavelength and higher energy levels, most Wood's lamps fortunately are small, inexpensive, safe, and easy to use. The usual instruments are small mercury vapor lamps fitted with a nickel oxide filter which satisfactorily transmits a beam of ultraviolet energy centered around the desired wavelength of 3,650 A. Hot quartz therapy machines and carbon arc machines emit near ultraviolet, and the wavelengths below 3,200 A can be screened by window glass, but there is also so much emission of white visible light that the pastel shades of fluorescence we wish to observe are masked. For the same reason, it is best to use a Wood's lamp in a dark room.

The most useful source of near ultraviolet for most of its medical applications is one of the small and inexpensive lamps.

Diagnostic Uses

Tinea Capitis.—The Wood's light has served its best known and greatest use in the diagnosis of tinea capitis, fungal infection of the scalp. Hairs infected with *Microsporum audouini* or *M canis* fluoresce a bright blue-green. Bits of lint, keratinous debris, and some topically applied agents will also fluoresce, but the color is weaker and blue-violet. It must be remembered that infections due to other dermatophytic organisms fluoresce poorly or not at all. The fluorescent hairs can be selected for direct microscopic examination and culture to confirm the diagnosis. This characteristic fluorescence can indicate the extent of involvement, assist easily and swiftly with case finding in a family or community, and permit recognition of a cure. Infections with *M audouini* are much less common now than 20 years ago, but the Wood's light is still extremely important in evaluating scalp lesions.

Erythrasma.—A superficial bacterial infection of the skin, usually involving intertriginous areas of the body, especially the toe-webs, erythrasma produces superficial scaling and cracking and sometimes marked pruritus while at other times none. The responsible organism produces a porphyrin that fluoresces a bright pink-orange under the Wood's lamp, which makes identification simple. The fluorescing material is soluble in water and therefore may not be present if the area has been washed recently.

Abnormalities of Porphyrin Metabolism.—Several varieties of disturbed porphyrin metabolism can be identified by Wood's light fluorescence of the appropriate substance in tissue or body fluids. Congenital porphyria can be confirmed by pink-orange fluorescence of the teeth, reddish urine, and the bone marrow.

Patients with acute intermittent porphyria excrete porphobilinogen in the urine, detectable with the Watson-Schwartz test, which does not require ultraviolet light. However, there are more sophisticated means of quantitating this test which do employ ultraviolet fluorescence.

The Wood's lamp can help make a diagnosis of porphyria cutanea tarda by fluorescing the excessive urinary excretion of uroporphyrin. A liver biopsy from a patient with this disorder usually fluoresces the pink-orange of uroporphyrin.

From the Department of Dermatology, University of Iowa College of Medicine, Iowa City.
Reprint requests to University Hospitals, Iowa City, Iowa 52240 (Dr. Caplan).

A recently delineated abnormality called erythropoietic protoporphyria, responsible for an interesting syndrome of cutaneous photosensitivity, can be documented qualitatively by Wood's light fluorescence of a blood specimen treated in the manner related by Rimington and Cripps.

Lesions of the Skin.—Certain lesions of skin or mucosa can be seen only poorly, if at all, with visible light. At times a greatly heightened contrast can be achieved by Wood's light illumination to display subtle accumulations of melanin in the oral mucosa or slight disturbances in the arrangement of vascular patterns or the keratinized surface layer. The contrast can make it much easier to perceive many early or fading eruptions, such as those due to lupus erythematosus, drug reactions, secondary syphilis, or other exanthems.

Under blacklight illumination, areas of skin involved with tinea versicolor appear decidedly lighter than the adjacent skin, or fluoresce a pale yellow-orange. This technique usually makes apparent many lesions that would otherwise be unrecognized and therefore untreated, which accounts partially for the notorious "relapse rate" or tinea versicolor.

Sakita and Utsumi used Wood's light successfully through a gastroscope to photograph the interior of the stomach. They found that their experimental technique provided sharper definition of ulcers and suspicious areas of the gastric mucosa.

Photoallergic Dermatoses.—Since some photoallergic dermatoses are triggered by long-wave ultraviolet light, it is possible to test for such sensitivity by exposure of the skin to appropriate sources. Many diagnostic Wood's lamps have an energy output too low to be of much service in this regard. Natural sunlight, carbon arc lamps, and hot quartz lamps, properly filtered with window glass to eliminate the rays below 3,200 A, are the ultraviolet sources customarily used for such testing. Those who have special needs may augment the energy output by building a source that contains several large fluorescent blacklight tubes.

Estrogenic Activity.—Purple fluorescence of the vulva has been correlated with levels of estrogenic activity. Prepubertal girls and menopausal women do not demonstrate fluorescence of the vulva, unless treated with exogenous hormone.

Enamel Disturbances.—In recent years it has become apparent that some instances of dental discoloration and hypoplasia are due to the administration of tetracycline during the time when tooth enamel is forming. Such affected teeth fluoresce a characteristic yellow color.

Therapeutic Uses

Effective therapeutic use of long-wave ultraviolet light is largely restricted to the treatment of vitiligo in combination with the systemic or topical administration of psoralen compounds. This type of treatment is tedious, not always useful, and occasionally hazardous. When employed in selected cases, the treatment is given with light sources of greater energy than is available in the customary commercial Wood's lamps, ie, with hot quartz lamps or natural sunlight.

A minor "therapeutic use" of the Wood's lamp is its employment as a placebo. In such a problem as multiple warts on a small child with a low pain threshold, painting the warts with a fluorescent substance (eg, thimerosal) and then "treating" them with Wood's light exposure can make an impressive effect on the child. Since placebos enjoy the reputation of a fairly satisfactory cure rate in the therapy of warts, this particular trick can sometimes be a useful adjunct.

Investigational Uses

Employment of ultraviolet light in scientific and industrial research is extensive. The following are some illustrative uses of long-wave ultraviolet light in medical investigation.

Daniels has reported a simple screening technique for determining the phototoxicity of almost any substance. Wood's light or other ultraviolet sources can be used to help clarify a diagnostic phototoxicity puzzle or to test dyes, cosmetics, topical medications, or other substances for trouble-making potential as phototoxic agents.

The selective fluorescence of malignant neoplasms, either spontaneously or after ingestion of a fluorescent substance selectively imbibed by the tumor, has tantalized many investigators. Tetracycline and its analogues have been used with some success in direct observation or exfoliative cytology of lesions or suspicious areas of a variety of organ systems (eg, mucocutaneous, pulmonary, urinary, gastrointestinal, and even in the central nervous system). A standardized, sufficiently reliable procedure is not yet available.

Wood's lamps have been employed by Harber and co-workers to demonstrate an abnormal photohemolysis in patients with erythropoietic protoporphyria.

Clark has shown that near ultraviolet light affects the development of tumors induced by artificial carcinogenesis.

Ultraviolet light used for bacterial sterilization generally has its wavelength centered around 2,500 A. However, Cohn and Middlebrook have demonstrated a striking sterilizing effect of near ultraviolet on *Staphylococcus aureus* and mycobacteria in droplet nuclei. They also showed that light of this wavelength produced an alteration in culture medium prior to inoculation with mycobacteria, such that it would no longer permit growth of the organism.

The study of inflammatory processes, blood flow, and tissue death can be aided by the intravenous administration of fluorescein, whose subsequent leakage from inflamed vessels or its failure to appear in an area can be readily detected with the Wood's lamp. Intra-arterial infusion of fluorescein, monitored with Wood's light, can delineate the peripheral area served by the vessel, and thus assure that cancer chemotherapeutic agents will arrive in the region desired.

Mustakallio and Korhonen have recently described a system for monochromatic ultraviolet photography of the skin, and have illustrated its utility in broadening our conceptions about what is usually perceptible.

If a topically applied agent happens to be fluorescent, such as some dyes, soaps, tars, or cosmetics, its persistence or "reservoir quality" can be assessed easily by repeatedly checking it with a Wood's lamp.

Students can receive an important lesson in the "migration" of substances or organisms from one place to another by handling an object primed by the instructor with a coating of anthracene; thirty minutes later the Wood's light will display unforgettably how widely the substance has disseminated over the individual and his local environment, and also how difficult it is to cleanse thoroughly the fingernail folds.

One of the most potentially valuable functions of a Wood's light examination is to provide a new "gestalt" for viewing subjects of interest. There is no way to predict what new observations may be possible when our eyes are made able to "see" phenomena not previously visible with our customary sources of "visible" light. Examination with Wood's light may not prove as fruitful to new discovery as examination with x-rays has been, but in certain regards, it may excel. We cannot know what we will see until we look.

(The omitted figures and references may be seen in the original article.)

NATURAL FOOD POISONS

A.D. Campbell, Ph.D., FDA Papers 1(7):23–27, September 1967.

Plants, animals, and micro-organisms can be sources of naturally occurring toxic substances which may remain in foodstuffs unless adequate precautions are taken to eliminate them. Many of the naturally occurring toxic components of food have received comparatively little attention, but acute (short term) and chronic (long term) toxicity have been recognized as results of man and animals eating foods contaminated with these substances.

Generally, through a trial-and-error process, man has been able to place plants and animals into safe and unsafe food categories. This trial-and-error process has been useful in eliminating those which produce acute toxicity; the results are usually sudden illness or death. However, the manifestations of chronic toxicity of some of these substances are not readily associated with the source; symptoms may occur after a considerable lapse of time. More sophisticated research studies are usually necessary to find the cause-and-effect relationships for chronic toxicity.

Plants may contain toxic substances, such as protein digestion inhibitors, toxic proteins (e.g., those found in castor beans), estrogenic substances, substances containing cyanides, solanine substances (e.g., toxins from potato sprouts), and a number of other toxic materials.

In some instances, the toxicant is at such a low level that it does not present a health problem when eaten; the estrogenic substances of soybeans are examples. In other instances, the toxicant can be inactivated by heating the foodstuff before it is eaten. For example, the protein digestion inhibitor of soybeans and the cyanide substances in lima beans are inactivated as toxicants by heating.

The toxic portions of some plants are usually removed and discarded. Those found in the skin and sprouts of potatoes which have been exposed to sunlight are thus avoided. Stalks of rhubarb are eaten and the toxic leaves are discarded.

Harvesting at the proper stage of maturity is a means of avoiding other plant toxicants. For example, unripened grapefruit contain a toxic substance which is not present in mature fruit. The use of selective breeding by the plant geneticist is another means of eliminating toxic substances from some plants. Gossypol, a toxic pigment of cottonseed, has been successfully bred out of cotton by this technique.

Some animals or animal products which are normally suitable as food can contain toxic substances under unusual circumstances. Oysters, clams, and other shellfish have been shown to contain a toxic substance known as "the paralytic shellfish poison" when they grow under adverse conditions. The puffer fish, considered a delicacy by some, contains a highly toxic substance in its skin and sex organs. Toxic animal metabolites (substances produced by the life processes) are known to contaminate some animal products when some toxic substances from molds are eaten by the animals. Detection by analytical means and discarding the contaminated lots may be the only means of avoiding them.

Micro-organisms (molds, yeasts, and bacteria) are known to produce toxic metabolites called microbial toxins. In considering microbial toxins the scientist is not concerned with the infectious nature of the micro-organism but with the toxic metabolites produced when the micro-organisms grow on foodstuffs. Examples of this class of toxic materials are the botulinum and staphylococcus toxins produced by bacteria. Less familiar are the mycotoxins produced by molds, such as the aflatoxins, the ochratoxins, and the estrogenic substances.

Mycotoxins have undoubtedly been with man since the beginning. However, they were not recognized as health problems until relatively recent years. The current emphasis in this field was stimulated in 1961 when a large number of turkeys died in England. British researchers investigated the "Turkey X" disease and found that the causative toxic material was a peanut meal coming from Brazil. They further related the toxic principle to the mold *Aspergillus flavus* and coined the word aflatoxin.

It is now known that the aflatoxins are produced by a number of molds, in addition to *Aspergillus flavus*. These are very potent toxins for some animals and the sensitivity varies over a considerable range for different species. Rainbow trout are the most sensitive animals that have been found so far. It is interesting to note that brown trout are relatively resistant compared to rainbows.

Ducklings are also quite sensitive, whereas sheep are the most resistant animals that have been studied. Primates are also sensitive to aflatoxins; however, nothing as yet is known about the toxicity to man. In addition to the acute toxicity of the aflatoxins, they have been found to be carcinogens for some animals.

It is not uncommon for the mycologist to isolate molds from cereal grains and other foodstuffs. Individual kernels are often found to be damaged by molds, but these are usually removed in the normal cleaning and processing of the grains. Only some molds produce toxic metabolites and only some strains of specific species produce toxic metabolites.

Many micro-organisms produce metabolites which have beneficial uses for man. The leavening effect of yeast in baked products is well known. Carbon dioxide (a metabolite of growing yeast) is entrapped in the dough or batter and produces the leavening effect. Other examples of useful microbial metabolites are the antibiotics and certain enzymes produced by yeasts, molds, and bacteria which find useful places in the processing and manufacture of food.

Sometimes the microbial metabolite can have both a good and a bad effect when fed to animals. The estrogenic substance produced by *Gibberella zeae* is of this nature. When this substance is administered to some farm animals at the proper dosage level, an enhanced growth rate is observed, and thus, it has a potential economic advantage to the farmer. However, when this substance is administered at higher levels, it can be troublesome in that it can cause abortion or prevent conception in breeding stock.

The Food and Drug Administration recognized the potential mycotoxin problem after Britain's encounter with the "Turkey X" disease. Scientists in the Division of Food Chemistry were immediately assigned to a research project to identify the problem. Moldy agricultural commodities were analyzed and in some cases aflatoxin was detected. This suggested that a potential problem might exist in this country. Research was initiated to develop reliable analytical methods for surveillance and control purposes.

Problems of this type require a multidisciplinary scientific approach, because the specific talents of

the microbiologist, the chemist, and the pharmacologist are closely interrelated.

Scientists in FDA's Divisions of Microbiology and Pharmacology joined the investigation. The microbiologists obtained aflatoxin-producing strains of mold and grew them in the laboratories to produce aflatoxins for further work by the chemists. The chemists developed techniques for the isolation and purification of the aflatoxins for chemical characterization and identification. These isolated aflatoxins were also used by the pharmacologists to investigate their toxicity and to develop sensitive toxicity methods.

At the same time, the chemists were devising more rapid and reliable analytical methods for the detection of aflatoxins in suspect agricultural commodities. The original methods required two and a half days for completion. The Division of Food Chemistry developed a rapid method which required only three and a half hours so a chemist could analyze eight or more samples in a day.

A small quantity of partially purified aflatoxins was supplied to a research team at the Massachusetts Institute of Technology for chemical structure research. They separated four aflatoxins and established their chemical structures. This valuable information was of great assistance to the chemists in their development of reliable chemical confirmation tests. The pharmacologists developed a reliable and sensitive chick embryo toxicity test.

While this phase of the research was going on, the FDA was in contact with members of the food industry, the U. S. Department of Agriculture, university research groups, and independent laboratories. Technical information was pooled and exchanged, expediting the collection and dissemination of technical data and information. This minimized duplication of efforts by the various groups and promoted a coordinated research effort on the problem.

As methodology was developing, technical personnel from industry, Government agencies, and universities were trained in the FDA laboratories on the most up-to-date techniques.

There has been a continued exchange of information between Britain, Canada, Holland, and other foreign countries from the start of this problem. In March of 1963, an international symposium was held at MIT on the subject of mycotoxins in foodstuffs. This provided an excellent opportunity to bring together investigators from all parts of the world to present scientific information and discuss this problem. The Food and Drug Administration, the National Institutes of Health, the U. S. Department of Agriculture, and a number of international organizations were participants. A subcommittee was established under the auspices of the International Union of Pure and Applied Chemistry to coordinate international efforts on the development of analytical methodology for the mycotoxins; a member of the Food and Drug Administration has been chairman of the subcommittee since its inception. Committees were formed in the Association of Official Analytical Chemists and the Association of Oil Chemists to further coordinate efforts in methods development. Members of the Food and Drug Administration have served on both of these committees.

A number of symposia dealing with mycotoxins have been held at scientific meetings, such as the Association of Official Analytical Chemists, Institute of Food Technologists, American Chemical Society, American Society of Microbiologists, and others in this country. Several of these have been of an international nature with recognized experts in the field of mycotoxins from many countries as participants. Professor Uritani of Nagoya University, Japan, world-renowned for his work in mycotoxins, was a guest speaker at the 1966 Annual Meeting of the Association of Official Analytical Chemists. A number of private meetings have been held with representatives of the food industry, U.S. Department of Agriculture research personnel, and Food and Drug Administration personnel in which current research was discussed and future research programs planned.

As a result of FDA's early efforts and through the cooperation of industry and the U.S. Department of Agriculture, contaminated peanuts have been diverted from food channels by a sound program for the prevention of aflatoxin-contaminated peanuts entering food channels.

Each lot of peanuts as it comes from the farm is examined and the lots likely to be contaminated with aflatoxins are analyzed. If the contamination is found too high, the lot of peanuts is used only for the production of peanut oil, because the refining process eliminates all traces of aflatoxins. If the peanut meal byproduct from this process is contaminated, it is used only for fertilizer. Processing of peanuts includes shelling, sorting, and cleaning; these processing steps are helpful in eliminating aflatoxin contamination. Aflatoxins analyses are carried out at further steps of processing, manufacturing, and on the finished consumer products. This cooperative effort between Government and

industry assures the wholesomeness of peanut products for sale to consumers.

The aflatoxin problem has not been confined to peanuts. An industry group concerned with the importation of brazil nuts into the United States was recently formed to deal with the aflatoxin problem in this commodity. This group was provided with technical information and assistance by the Food and Drug Administration and the U.S. Department of Agriculture. Laboratory equipment for the analysis of the aflatoxins was purchased and taken to Brazil to expedite the efforts to prevent the shipment of aflatoxin-contaminated brazil nuts into this country. The group was successful in encouraging the Brazilian Government to establish a laboratory which will analyze exports of brazil nuts and certify the absence of aflatoxin. This is another excellent example of the fine cooperation which has existed in attempts to cope with this problem in a manner which protects the consuming public.

Protection of the public health, of course, is the incentive for the Food and Drug Administration to initiate and coordinate such an effort. In the case of aflatoxin in peanuts, it was possible to protect the public through combined research and self-regulation efforts. However, it was necessary from the beginning for FDA to recognize that peanut products would have to be handled like any other food adulterated because of contamination by fungal infestation, or by toxins elaborated by fungal organisms. For that reason, it was necessary to develop reliable biological and chemical tests to provide proof of adulteration for regulatory purposes.

For practical reasons, these tests should be specific, simple, rapid, and yet be sufficiently sensitive and accurate to measure small but significant quantities of deleterious substances. As already indicated, sensitive and reliable chemical methods, chemical confirmatory tests and toxicity tests suitable for regulatory purposes, have been developed.

FDA does not assert that any one of these methods meets all ideals of accuracy, precision, sensitivity, and specificity. Nevertheless, when considered as a battery of tests, they give consistent and reliable information.

Current analytical methods are capable of detecting and confirming the presence of aflatoxins in a range well below 50 parts per billion of product. At present, there is no pharmacological data indicating a safe level of aflatoxin in man. Since they are carcinogens for some animals, no tolerance can be set for these substances. Any demonstratable concentration of aflatoxin is proof of excessive contamination with fungal toxins.

A new dimension in the potential for a health hazard from aflatoxin has appeared. It has recently been reported by Oregon State University researchers that an interaction exists between the cyclopropenoic fatty acids and aflatoxins when fed to rainbow trout. The cyclopropenoic fatty acids are normally present in cottonseed oil. They do not produce liver tumors in the trout when fed alone; however, when they are fed along with the aflatoxins, tumors are produced in the trout at much lower levels than when the aflatoxins are fed alone.

This important finding illustrates the potential of interrelationship between naturally occurring food poisons and suggests the possibility of other food constituents having an effect upon the sensitivity of animals to the aflatoxins and other naturally occurring toxins.

The development of a screening method which will detect the three recognized classes of mycotoxins (aflatoxins, ochratoxins, and the estrogenic factor of *Gibberella zeae*) in foodstuffs is nearing completion in our laboratories. This will provide a timesaving means for screening of foodstuffs for the presence of some of the mycotoxins. Validation studies are presently being conducted. When these studies are complete, this screening method will offer a valuable tool for the Food and Drug Administration's District laboratories and research laboratories for expediting the collection of data on the mycotoxin problem.

A simple, rapid toxicity test using brine shrimp for the aflatoxins is nearing completion. Brine shrimp eggs are readily available in any pet shop. When these eggs are placed in sea water, they hatch in 24 hours to produce shrimp barely visible to the naked eye. These newly hatched shrimp are quickly killed when exposed to aflatoxin. Considerable interest has been shown in this test, because it can be completed in two days in most laboratories.

We now know that *A. flavus* produces several toxins, in addition to the four originally recognized aflatoxins. Analytical methodology is currently under development which, when completed, will provide a means for the detection of these other toxins so that surveillance can be carried out on agricultural commodities to establish whether or not they may present a health hazard.

Research programs are underway in the Food and Drug Administration's laboratories to seek out other mycotoxins which may be a health hazard to the

consumer. Many toxic substances undoubtedly remain to be discovered in natural food products.

Much has been learned by the scientific community from the great amount of research which has gone on in many laboratories since the aflatoxins were discovered in 1961. This information has been quickly put to use to protect the health of the people throughout the world. These studies indicate that much is still to be learned about naturally occurring food poisons. Only through concerted research efforts of many laboratories will the basic scientific information be obtained for a sound evaluation of this newly recognized problem.

(The omitted figures may be seen in the original article.)

MEDICAL ABSTRACTS

EXPERIMENTAL ASPECTS OF HEPATIC REGENERATION

N.L.R. Bucher MD, New Eng J Med 277(13): 686–696, Sept 28, 1967.

An attribute of the liver that continues to fascinate investigators is its latent capacity for growth. Mature liver cells are long-lived and, in rats and mice at least, may even survive for the adult life of the animal (approximately 1 mitosis is seen in 10,000 to 20,000 hepatocytes, about enough to keep up with the continuing body growth in these species). The simple expedient of partial hepatectomy, a well tolerated and highly reproducible operation with essentially no mortality, sets in motion a burst of astonishingly rapid growth. This growth is precisely regulated; it tapers off and finally ceases when the deficit has been restored. The process affords a fine opportunity for examining the controlled transition between the extremes of nongrowth and active proliferation. The mode of operation of the regulatory mechanisms remains tantalizingly obscure, but much has been learned about the growth process itself.

A RETROSPECTIVE SURVEY OF 498 PATIENTS WITH MALIGNANT MELANOMA

R. McLeod, et. al., Surg Gynec Obstet 126(1): 99–108, Jan 1968.

The clinical findings and results of treatment were analyzed for 498 patients with malignant melanoma. The series included patients with lesions in all primary sites other than the eye, as well as those who presented with metastatic deposits but no identifiable primary lesion.

All patients were white, and there were more males than females. Lesions were commonest in the 30 to 59 year old age group. Approximately 17 percent of the patients presented with clinical evidence of metastases. About 9 percent of prophylactic node dissections were reported to show histologic evidence of metastatic deposits. The 5 year survival rate was 54.7 percent and the 5 year cure rate 48.6 percent. These figures support the view that patients in Queensland presented for treatment of melanomas at an earlier stage than did those in other countries.

Those patients with lesions of the extremity who underwent a prophylactic node dissection tended to survive longer than did those who were observed for evidence of metastases, but the figures did not reach a significant level.

DERMATOGLYPHIC PATTERNS IN PATIENTS WITH SELECTED NEUROLOGICAL DISORDERS

F. Rosner MD, F. S. Steinberg MS, and H. A. Spriggs BA, Amer J Med Sci 254(5): 695–707, Nov 1967.

A study of dermatoglyphics in patients with various neurological disorders has been carried out. Dermatoglyphic patterns in 267 Caucasian patients with Down's syndrome (Mongolism) are described. Abnormalities in such patients include a preponderance of ulnar loop patterns on the fingers particularly the index and middle fingers with a corresponding diminution in arches and whorls, a shift of radial loops from the index to the ring and little fingers, the presence of small ulnar loops (12 ridges or less), on the ring and little finger, an increased incidence of third interdigital and hypothenar area

patterns, a greater proportion of simian lines, a lower incidence of fourth interdigital area patterns and greatly enlarged atd angles.

Minor deviations from normal were found in the dermatoglyphic features of 341 patients with phenylketonuria, idiopathic epilepsy, primary hydrocephalus and microcephalus. The numerous distinctive features diagnostic of Down's syndrome, however, were not present in patients with the aforementioned conditions. Two features: the presence of a simian line on both hands and the absence of a pattern in the fourth interdigital area on the left hand differed significantly in patients with idiopathic epilepsy and phenylketonuria from the control subjects.

Although most cases of Down's syndrome are clinically obvious, several dermatoglyphic features are very useful diagnostically in a questionable case. However, these features seem to be of little value in the diagnosis of other selected neurological disorders.

PSYCHOLOGIC RESPONSE TO COLECTOMY

R. G. Druss MD, J. F. O'Connor MD, J. F. Prudden MD, and L. O. Stern, Arch Gen Psychiat 18(1): 53–59, Jan 1968.

The physical and emotional adaptation of 41 patients who required total colectomy and permanent ileostomy for ulcerative colitis are reported.

All but one patient stated that their general health was good to excellent. Most patients felt that having an ileostomy was preferable to living with severe chronic ulcerative colitis. No patients evidenced a symptom alternation, and neither psychosis nor the establishment of a new psychosomatic target organ occurred following colectomy.

The good results in the areas of school, work, and social activities were not always duplicated in a sense of personal well-being. Almost half (46%) of the patients described various subjective problems with their ileostomy such as sexual problems, fears of "accidents," odor, "straining" themselves, and embarrassment. Most patients indicated that acceptance of the ileostomy by key figures in their life (family, employer, etc) was essential for successful adaptation on their own part. When used, visits by the local ileostomy club members were considered most helpful, both in training prospective and new patients, and in providing successful models for identification.

The surgeon must be aware of the many emotional difficulties related to the surgery that a patient may be experiencing, yet be hesitant to verbalize, in spite of apparently good overall functioning.

PHARMACOLOGY OF ANIMAL VENOMS

F. E. Russell MD, Clin Pharmacol Ther 8(6): 849–873, Nov-Dec 1967.

The animal venoms are the most complex of all the poisons. The study of their physiopharmacological activities and the autopharmacological responses they produce is one of the most important new fields in toxicology. The value of venoms as tools in biochemistry and perhaps their use in the treatment of disease is also becoming apparent. Finally, the injuries produced by venomous animals are of considerable medical importance. Some 35,000 to 50,000 persons a year die from the bites or stings of these animals, and perhaps some 10 million persons are poisoned by them each year. With these things in mind, the author has attempted to review some of the more important chemical and pharmacological properties of the toxins of representative poisonous species from the marine fauna, terrestrial snakes and arthropods. Some consideration has also been given to the venom apparatus of several species and to the medical problem of envenomation.

DENTAL SECTION

PALATAL PAPILLARY HYPERPLASIA

G. O. Lambson and R. R. Anderson, J Prosth Dent 18: 528, 1967.

The authors state that with rare exception papillary hyperplasia of the hard palate occurs in patients who wear *complete* maxillary dentures. Recommended treatment of this lesion is supraperiosteal resection. Complete recovery from this treatment may occur in one month but usually takes longer accompanied by some pain and complication in eating.

A survey of 301 male denture-wearing domiciliary residents of the Veterans Administration Center, Wadsworth, Kansas, was conducted. The mean age of the maxillary denture wearers was 63.1 years. The mean length of time that they were edentulous was 16.9 years. The mean number of years that the patients wore their current dentures was 5.48 years. The survey population was divided into two groups: those who wore their dentures during the waking hours only, (48%) none of whom had papillary hyperplasia; and those who wore their dentures 24 hours a day, (52%) 20% of whom had the disease.

Other information derived from the data collected was:

1. The age of the patient was not significant in relation to the disease.

2. As a group, patients with the disease had been edentulous longer and their dentures were older than those without the disease.

3. Cleanliness of the dentures decreased with round the clock wearers, and reached a low with patients who had papillary hyperplasia.

4. No connection was made between palatal reliefs and the disease.

The conclusions drawn by the authors from this study are that dentists should instruct their patients to remove complete dentures from their mouths for several hours daily to prevent papillary hyperplasia. In addition, a patient's oral tissues and his dentures should be periodically examined to prevent the prosthesis from becoming a pathogen.

(Abstracted by: CDR Robert W. Elliott, DC USN.)

PRIMARY ORAL CARCINOMA WITH PULMONARY METASTASES: REPORT OF CASE

J. M. Doner, E. L. Granite, G. Laboda, and A. Finkelman, J Oral Surg 25(2): 168–173, March 1967.

Examination of a 53-year-old Caucasian male with a six month history of pain and swelling revealed a large, fulminating mass in the right floor of the mouth. Radiographs showed extensive bony destruction of the body and ascending ramus of the right mandible. A skeletal survey and chest x-ray failed to demonstrate any evidence of metastatic disease. A histologic diagnosis of poorly differentiated squamous cell carcinoma was obtained from an incisional biopsy and the patient was treated with a combined course of methotrexate and cobalt radiation. Four months later the tumor had decreased greatly in size and radiographs showed calcification of the right body and ramus of the mandible. Routine chest films, however, revealed a nodular lesion in the right middle lobe of the lung. The lung lesion was resected during an exploratory thoracotomy and a diagnosis of metastatic carcinoma, consistent with origin in the mouth was established by histologic examination. Radiographic follow-up one year later revealed a metastatic nodule in upper left lobe of the lung, but no further evidence of bony destruction of the mandible. Fourteen months later the patient expired and autopsy examination revealed metastatic nodules in both lungs and throughout the liver. The histomorphology of the lung lesions was identical to that of the oral tumor.

(Abstracted by: CAPT Geogre H. Green, DC USN.)

OSTEOGENIC SARCOMA OF THE MANDIBLE: REPORT OF CASE

C. L. Hughes, J Oral Surg 25(2): 164–167, March 1967.

A 65-year-old negro man presented with a four month history of persistent pain in the left mandible and numbness of lower left lip of two months duration. Previous extraction of the lower left first molar, followed by extraction of the second pre-

molar, and finally a course of antibiotics had failed to bring relief. Radiographs revealed a lesion extending from the premolar region to the ascending ramus of the mandible. The "motheaten" appearance was suggestive of osteomyelitis and the patient was treated with antibiotics. Histologic examination, however, disclosed the lesion to be an osteogenic sarcoma and a left hemimandibulectomy was performed. The early symptoms of osteogenic sarcoma of the jaws may clinically and radiographically simulate chronic osteomyelitis. A biopsy of all suspicious cases is indicated in order to prevent delay in definitive treatment and to enhance the chance of survival.

(Abstracted by: CAPT George H. Green, DC USN.)

PERSONNEL AND PROFESSIONAL NOTES

RESEARCH IN CLINICAL OPERATORIES DESIGN AND EQUIPMENT

On 31 January and 1 February 1968, the Naval Dental Research Institute, Naval Training Center, Great Lakes, Illinois, held a conference to review the accomplishments of research project entitled, "Research in Clinical Operatories Design and Equipment," and further, to consider future planning of dental facilities and treatment programs in the Navy.

The two-day conference was a follow-up to conferences held in 1964 and 1965 which identified problems in clinical practice that needed specific attention in research and development. One of the recommendations of the 1965 conference was that there be established a research center for the research, development, testing and evaluation of new dental office design, equipment, procedures and utilization of auxiliary personnel for application to the Naval Dental Service. In addition the 1965 conferees recommended there be a full scale testing of the hypothesis that the total practice of dentistry can be accomplished using an aseptic technique in a dental surgical clean environment with increased efficiency and greater ease to the patient, the dental officer and the dental technician. As a result, the Clinical Research Division of the Naval Dental Research Institute was established and research unit number M4114.04–3002 was activated. An experimental dental clinic, equipped and designed to meet the specific objectives outlined by the conferences began operation in February 1967. Over 5,000 patients were treated in these experimental facilities by 36 different dental officers and 27 technicians.

Fifty invited senior dental officers of the three military services attended. The data and evaluation of the findings as well as recommendation of the conferees, relative to this new concept in the practice of dentistry, is being summarized for publication at a later date.

STERILIZATION OF MOUTH MIRRORS

This Bureau is in receipt of numerous complaints concerning the rapid deterioration of mirrors when sterilized in dry heat ovens. This objection may be overcome by dipping the mirrors in a protective emulsion* and sterilizing in an autoclave. It is reported that mirrors handled in this manner will last indefinitely.

* Kerr's Proclave Emulsion.

NURSE CORPS SECTION

DIABETIC CLINIC AT NAVAL HOSPITAL, OAKLAND, CALIFORNIA

The Diabetic Clinic at Naval Hospital, Oakland is a relatively new clinic. In an effort to obtain the maximum in patient care, the professional team from the clinic is currently visiting active diabetic clinics in the Oakland area. The naval Hospital team consists of two staff doctors, a dietician, and a Navy nurse.

During these visits, the team meets with the doctors, nurses and dieticians of the various clinics, discusses physical facilities, educational programs, and patient care activities. Group conferences are held and individual conferences between members of the different professions involved. Following each visit the Naval Hospital Oakland team conducts meetings to discuss any observations.

To date, the Oakland team has been the guests of Highland Hospital, Oakland, and Stanford Medical-Specialties Clinic, Palo Alto, California.

PANEL DISCUSSION ON PROVIDING SUPPORTIVE CARE FOR THE HOSPITALIZED CHILD

A panel discussion was held recently during the Pediatric Nursing Conference for Nurse Corps officers at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland on the topic of providing supportive care for the hospitalized child.

A summary of the discussion follows. Specific information is needed concerning the family background of the hospitalized child and is usually obtained by interviewing the parents and other members of the family in order to determine:

1. Individual needs of the child.

2. The extent to which the child has been prepared for the hospitalization. Is this the first time? Is it a repeated visit? It may be that the parents should not inform the child until just before he comes to the hospital or they should inform him well in advance.

3. Is the child used to having other children around him?

4. What is the child's relationship to his doctor? Is he afraid of him or have they made friends?

5. What are the childs eating and bedtime habits? Does he have certain routines or a special vocabulary?

During the interview with the parents certain information should be given to the parents concerning what the parents can bring the child in the hospital—toys—food, etc., visiting hours and meal hours.

The corpsman's role in providing supportive care to the child also was discussed. This role, it was determined, could at times be that of a father image. The importance of the corpsman establishing good rapport with the child, being kind and gentle in his actions, and letting the child know that he is on his side was emphasized. Supportive care according to the panel involves more than words on the part of each staff member—it involves actions namely:

Showing the child that you care
Being confident in your ability to care for him and having him realize this
Spending time with the child in play, etc.
Letting the child get acquainted with you and the staff
Explaining what is going to be done to the child before it is done
Truth and honesty in every action and speech
Encouraging the family and friends to send mail
Letting the child have his favorite toy
Encouraging the child to think about what he will do when he does get to go home

Supportive care is very individualized and it is essential that the nurse must know the child and his parents in order to provide this type of care. The child should be met on his own level. Remember to talk to the child and not at him. In addition to this, communication between staff personnel on different shifts is very necessary and important for continuity of the supportive care of the hospitalized child.

RESERVE SECTION

ANNOUNCEMENT OF COURSE IN AEROSPACE MEDICINE

Current Aerospace Medicine—Naval Aerospace Medical Institute, Naval Aerospace Medical Center, Pensacola, Florida

Description—A two week course designed to familiarize Reserve Medical Department officers with the latest concepts of Aerospace Medicine. The course will cover three major areas: current basic and clinical research, medical aspects of flight training, and operational Aerospace Medicine. All personnel who desire ACDUTRA at this activity are encouraged to apply for this course since training duty billets will not generally be available at any other time during the year.

Eligibility—2105, 2305 (other than psychologists), 2905, and 8175 officer personnel.

Report To—Commanding Officer, Naval Aerospace Medical Institute, prior to 0800, convening date.

Quota Control—Training Activity

Convening—15 July 1968

PREVENTIVE MEDICINE SECTION

NEW IMMUNIZATION INSTRUCTION

The tri-service directive on immunization methods and procedures has been revised and is now designated in the Navy as BUMED Instruction 6230.1E, dated 21 December 1967.

Significant changes in this publication include: granting of waivers; recording of smallpox vaccination; schedule and/or dosage change in typhoid, yellow fever, plague and other vaccines; and establishment of a new immunization certificate.

Copies have been mailed to an extensive Navy/Marine Corps distribution list. Additional copies may be obtained by Navy/Marine Corps addressees from: Supply and Fiscal Department (Code 514.32), Naval Station, Washington, D. C. 20390.

PROPOSED REVISION OF THE INTERNATIONAL SANITARY REGULATIONS

PANSABU WHO Wkly Epid Rpt XL(3):13, Jan 17, 1968.

The Committee on International Quarantine of the World Health Organization, met in Geneva, Switzerland, from 28 Nov to 7 Dec 1967. It prepared a draft of a revision of the International Sanitary Regulations, which will be presented for the consideration of the World Health Assembly in May 1968. Before making its recommendations, the Committee deliberated on comments from various governments and from the International Civil Aviation Organization, the International Air Transport Association, and the Inter-Governmental Maritime Consultative organization, as well as the report of the Director-General of WHO on the present Regulations. The proposed changes are principally concerned with removal of typhus and relapsing fever from the list of quarantinable diseases and the establishment of a new category of diseases requiring international surveillance, adequate staffing of quarantine services at international ports and airports and the provision of such services at frontier posts when necessary, and standards for sanitation and vector control.

MUMPS VACCINE

Los Angeles Co, Health Dept Morb & Mort Rep Dis, Jan 15, 1968.

Recommendation of the Public Health Advisory Committee on Immunization Practices Meeting of 12 October 1967.

Introduction

A live attenuated mumps virus vaccine has recently become available for general use. It is appropriate to describe the circumstances under which this vaccine might be considered for use.

Mumps, one of the common communicable diseases, is observed with greatest frequency in young school-age children although 15% of reported cases occur after the onset of puberty. Overt evidence of central nervous system disease with sequelae is rare, while meningeal involvement appears to be common. Orchitis has been reported in up to 20% of the clinical mumps cases occurring in post-pubertal males. Symptomatic involvement of other glands and organs is observed less frequently. All naturally acquired mumps infections, including the estimated 30% which are subclinical, confer durable immunity.

Live Mumps Vaccine

Live mumps vaccine is prepared in chick embryo cell culture. It produces an inapparent, noncommunicable infection following administration. Febrile reactions and mumps-like symptoms have not been associated with the vaccine.

More than 95% of susceptible vaccinees develop detectable antibodies after vaccination, although titers are lower than those induced by natural infection. The pattern of antibody persistence parallels that seen following clinical mumps although at a lower level. The long-term duration of antibody is unknown at the present time; individuals have been observed for only 2 years following vaccination because the vaccine is a recent development. Excellent protection against naturally occurring mumps has been documented in vaccinees for the first year

after vaccination. Limited data on natural exposure during the second year indicate continuing protection.

Recommendations for Vaccine Use:

a. *Live mumps vaccine* may be considered for use in children approaching puberty, in adolescents, and in adults, especially males, if they have not had mumps. The vaccine is not specifically contraindicated for younger children, but until more information on the duration of immunity is available, the vaccine is not recommended for routine use. Furthermore, mumps immunization should not be allowed to compromise the effectiveness of public health programs of already established importance.

b. *Age*. Live mumps vaccine should not be administered to children less than 12 months of age because of the possible persistence of interfering maternal antibody.

c. *High Risk Groups*. Epidemic mumps can be particularly disruptive to normal routine in large groups of susceptible individuals. Children living in institutions, for example, might benefit from vaccination against the disease.

d. *Prevention of Natural Mumps Following Exposure*. Adults and adolescents who are susceptible to mumps by clinical history present a perplexing medical problem when exposed to mumps. It is not now known if live mumps vaccine will provide protection when administered after exposure. There is no contraindication to its use at that time.

Precautions in Using Live Mumps Vaccine:

a. *Severe Febrile Illnesses*. Vaccination should be postponed until the patient is completely recovered.

b. *Marked Hypersensitivity to Vaccine Components*. Mumps vaccine is produced in chick embryo cell culture and should not be given to persons hypersensitive to ingested egg proteins. The vaccine contains small amounts of neomycin, so it should not be given to individuals known to be sensitive to this antibiotic.

c. *Leukemia, Lymphomas, and Other Generalized Malignancies*. Theoretically, attenuated mumps virus infection might be potentiated by other severe underlying diseases, such as lymphomas and generalized malignancies.

d. *Altered Resistance From Therapy*. Steroids, alkylating drugs, antimetabolites, and radiation may predispose to untoward complications due to altered resistance.

e. *Pregnancy*. Mumps virus infection is not known to exert any untoward effects on the developing fetus. It is reasonable on theoretical grounds, to avoid using the live mumps vaccine during pregnancy.

Simultaneous Administration of Live Mumps Vaccine With Other Antigens

In order to evaluate the live mumps vaccine adequately, its simultaneous administration with other vaccines should be deferred until results of controlled clinical investigations are available. Until then, it is recommended that mumps vaccination be separated from other immunization procedures by about one month whenever possible.

INFECTIONS CAUSED BY MIMEAE, WITH SPECIAL REFERENCE TO MIMA POLYMORPHA: A REVIEW

S. Y. Alami, et. al., Amer J Med Sci 252(5): 67/537–74/544, Nov 1966.

The word "mimeae" is of Latin origin, "mimus," which means "to mimic." The name was given by DeBord in 1939 to this group of organisms because of the tendency of Mimeae to mimic Neisseria organisms clinically and bacteriologically. The species' name, polymorpha, expresses their pleomorphic nature; examination of direct smears and smears from solid medium cultures reveals a predominance of Gram-negative diplococci, while Gram-negative rods dominate smears from fluid culture medium. In contrast to Neisseria species, however, they are nonfastidious; they grow aerobically at 37° C. on ordinary laboratory medium under normal atmospheric pressure conditions.

The Mimeae are Gram-negative, pleomorphic, encapsulated organisms of variable motility with *M. polymorpha* being nonmotile. They may retain partial Gram-positiveness and often show bipolar staining. They are not fastidious and grow well aerobically on ordinary culture media under normal atmospheric conditions with the formation of small, white-greyish, convex, slightly raised, smooth colonies. On eosin-methylene blue (EMB) medium, they tend to appear with bluish-purple coloration. Diplococcal forms are present on direct smears and predominate in colonies grown on solid culture media, whereas rods and filamentous forms are present in fluid culture media. The various species are partly differentiated by their ability to ferment carbohydrates. In general, however, they have a low

metabolic activity similar to that of the alkaligenes group from which they are differentiated by their nonmotility. They essentially fail to reduce nitrates to nitrites, which differentiates them from other enterics; but atypical strains of nitrite producers may be encountered. On triple-sugar iron (TSI) medium they give an alkaline reaction without hydrogen sulfide production. They are indol, methyl-red and Voges-Proskauer negative, but citrate utilization depends on the genus tested, with *Mima polymorpha* being negative. Mimeae fail to split urea, which helps to differentiate them from Proteus species. They can be differentiated from Neisseria by oxidase reactions (with the exception of *M. polymorpha var. oxidans*) and serologic tests.

Studies on the *in vitro* susceptibility of the organisms to various chemotherapeutic agents reveal them, in general, to be resistant to penicillin but susceptible to the broad-spectrum antibiotics, especially oxytetracycline and chlortetracycline. The resistance pattern to sulfonamides is variable. However, the reports in the literature concerning susceptibility are so divergent that no conclusion can be predicted with any degree of accuracy for the genera and the individual strain tested.

Knowledge of the response of Mimeae to physical and chemical agents is sparse. Apparently, however, they fail to survive heating at 60° C. for 30 minutes in either milk or broth cultures. They grow equally well at room temperature (20° C.) and at 37° C.

Epidemiology and Pathogenesis. DeBord first encountered Mimeae in smears from patients with a diagnosis of gonorrhea, the causative organism originally having been considered to be *N. gonorrheae*. Later, he isolated them from cases of conjunctivitis, vaginitis, urethritis, meningitis and from the normal vagina. Since then they have been recovered by several workers from many human sources (representing various age groups) including: vagina, urethra, urine and conjunctiva, sputum, skin and wounds, blood, synovial fluid, petechiae, bone and bone marrow, pleural effusion, ears, and other sources.

Although Mimeae have been incriminated as causative agents of conjunctivitis, vaginitis, and nongonorrheal urethritis, they have also been recovered from these sites in healthy individuals which has led some to question their role as pathogens at these sites. Several workers have reported recently on the frequency of isolation of these organisms from the skin of normal males. Nevertheless, Mimeae, *M. polymorpha* being the most common, have been isolated from well documented cases of meningitis or septicemia, or both these conditions, from endocarditis cases, a case of cerebral abscess, and from some cases presenting a clinical picture of Waterhouse-Friderichsen syndrome. Also, they have been incriminated etiologically in lobar pneumonia and in otitis media.

The high incidence of these infections in newborn infants was suspected to be due to the opportunities for infants' exposure to these organisms in the birth canal. Yet, investigators were unable to isolate *M. polymorpha* from the vagina or to demonstrate specific serum antibody in the mother. They suggested, however, that the poor defense mechanisms of the young infants against Gram-negative organisms of low virulence may be a factor contributing to infection in this age group.

The upper respiratory tract is presumed by some to be the portal of entry in systemic Mimeae infections. In one case of bacterial endocarditis with multiple bacterial emboli, the prostate was thought to be the source of infection. Transmission from man to man is suggested by 2 cases of meningitis in soldiers in intimate contact and the occurrence of meningitis in premature twins. This issue, however, is difficult to evaluate in the light of our present knowledge of the normal habitat of the organisms in humans. Whether the Mimeae are primarily enteric, skin, or respiratory dwellers is still obscure. On the other hand, they have also been isolated from several environmental sources. Recently, Mimeae were encountered in dairy products during routine bacteriological examination. Several authors suggested a ubiquitous existence similar to that of staphylococci. These workers, along with others speculated that Mimeae may be considered as pathogens of low virulence which infect host of low resistance to produce often minor rather than devastating infections. Recently, others considered them to be opportunistic pathogens with a highly variable degree of virulence.

Few studies have been reported dealing with the pathogenicity of Mimeae for experimental animals. One investigator found that the injection of 0.5 ml of a 24-hour broth culture intraperitoneally, but not subcutaneously, was lethal for guinea pigs. Another reported their pathogenicity for mice by the intraperitoneal route; diplococcal forms were recovered from mice injected with broth cultures containing predominantly rod-shaped forms. Considerable variation in the pathological findings in different species of experimental animals following intraperitoneal and intravenous injection of different quantities of broth cultures of Mimeae has

been reported. The differences may be due in part to improper identification of the organisms, to technical variations or to bacterial dosage, animal size and age differences.

Clinical Manifestations. Meningitis caused by Mimeae presents with a clinical picture indistinguishable from that of cases due to *N. meningitis.* One recent case seen in the author's clinic was that of a 4-year old girl, who was initially considered by the family physician to have measles, presented with the picture of meningococcal meningitis. She was febrile, lethargic, exhibited nuchal rigidity and hemorrhagic petechiae over the skin. Direct smears of the cerebrospinal fluid revealed Gram-negative diplococci. The patient expired 20 hours after admission in spite of the treatment with adequate doses of penicillin and a sulfonamid. Subsequent examination of the spinal fluid and blood cultures revealed the agent to be *Mima polymorpha var. oxidans*, which was resistant to penicillin, sulfonamides and streptomycin, but sensitive to chlortetracycline, oxytetracycline, kanamycin and novobiocin. Likewise, bacteremia due to Mimeae appears to have a course typical of blood stream infections due to other Gram-negative bacteria. Fulminating septicemias, some of which have been accompanied by high fever, marked toxicity, vascular collapse and petechiae, suggestive of the Waterhouse-Friderichsen syndrome with hemorrhage in the adrenals at necropsy, have also been reported. Mimeae have been isolated from the urine in numbers exceeding 100,000 organisms per ml. of urine in patients with urinary tract infections. In cases of pneumonia, gonorrhea, urethritis, vaginitis, wound infections and other reported sites of infection, the clinical picture appears to be also similar to those caused by the more commonly recognized agents. Mimeae have been isolated from patients with subacute bacterial endocarditis whose course extended as long as 2 years.

Prognosis of the patient with these clinical pictures is variable and is influenced by the site of infection, the age and general condition of the patient. The relatively high incidence of Mimeae infections in premature, newborn and young infants has been noted. Patients in any age group are susceptible especially if debilitated by serious underlying disease such as malignancy, burns and chronic renal disease and those receiving therapy which suppresses body defense mechanisms such as cortisone, anti-metabolites and radiation. Furthermore, prognosis also appears to be related to the severity of the infection, to the capacity with which the offending organism is isolated and identified, and to the administration of an appropriate antibiotic early in the course of the disease process. This impression is partly reflected in the recent report of 2 cases of meningitis caused by *M. polymorpha var. oxidans,* with variable severity of the infection and sensitivity of the organism to antibiotics.

Diagnosis. The diagnosis is established by the recovery and identification of the organisms from the appropriate specimen. This largely depends on a high index of suspicion by the physician and the awareness of the laboratory personnel of the existence of Mimeae. Otherwise, the chances of making the correct diagnosis are poor. For example, one researcher submitted a culture of *Mima polymorpha,* isolated from one of his cases, to 13 bacteriological laboratories, and alarmingly none identified the organism correctly. The identification and differentiation of Mimeae from Neisseria species, with which they are most frequently confused, is essential and constitutes more than an academic interest since they differ greatly in their susceptibility to antibiotics. The failure to suspect and to identify the penicillin-resistant Mimeae may lead to serious, occasionally fatal, consequences. Identification of *Mima polymorpha var. oxidans* and other species depends on the following criteria and procedures.

1. Recognition of the pleomorphic nature of the organisms: Gram-negative diplococci, or cocci in various groupings, appear on direct smears of specimens, for example, cerebrospinal fluid, while short, Gram-negative rods predominate in broth cultures.

2. The nonfastidious nature of the organisms, as compared to Neisseria species, permits their growth overnight on ordinary laboratory media under aerobic and normal atmospheric pressure conditions. Recently described is a medium that is suitable for the growth and identification of Mimeae and other Gram-negative nonfermentative bacilli of medical importance.

3. Low metabolic activity and failure to reduce nitrates.

4. Negative oxidase reaction, except in the case of *M. polymorpha var. oxidans.*

5. Subsequent antibiotic-susceptibility studies.

6. Pathogenicity for experimental animals, for example, mice.

7. Finally, when available, the use of type-specific antisera will easily confirm their identification and differentiate them from Neisseria organisms.

Treatment. In general, most strains of Mimeae have been found to be sensitive to tetracyclines and resistant to penicillin and streptomycin. Penicillinase production by 80 penicillin-resistant strains of Mimeae was reported. The susceptibility of Mimeae to chloramphenicol and sulfonamides is reportedly variable. Similar findings, but based on more limited studies, are reported in relation to erythromycin, novobiocin, neomycin, kanamycin, bacitracin and polymyxin. Recently, workers found sodium colistimethate, kanamycin sulfate, and others to a lesser extent, to be the most consistently effective therapeutic agents *in vitro*, while, in contrast to previous reports, the organisms were found to be unusually resistant to tetracyclines. With this controversy and confusion in the literature, many workers have suggested the need for more extensive evaluation of larger series of strains of Mimeae.

Summary. The tribe Mimeae includes a group of organisms which are encountered in a variety of human infections, including such serious ones as meningitis and septicemia. *Mima polymorpha* is the species most commonly encountered and, like other members of the tribe, is frequently confused with other organisms, especially Neisseria species.

The following conclusions may be drawn from a review of the literature.

1. Mimeae, especially *Mima polymorpha,* are pleomorphic, Gram-negative organisms that are capable of human disease production.

2. Diagnosis of infections due to these organisms depends on the recognition of their existence and pathogenicity, both by the attending physician and the laboratory personnel.

3. In general, they appear to be resistant to penicillin and sulfonamides and their susceptibility to other antimicrobial agents is variable. The choice of therapeutic agent should be based on the *in vitro* susceptibility of the individual strain isolated. Before this information is available, tetracycline should probably be utilized in serious infections suspected to be due to Mimeae. Continuing studies with newer antimicrobial agents may modify this recommendation, however.

4. There is persistence of confusion and uncertainty as to the position of the tribe Mimeae in the taxonomic system and the true identity of its members, which requires further evaluation and clarification.

Editor's Note: Space does not permit the printing of the extensive bibliography appended to the original article. Interested Medical Department personnel are urged to consult the original in the journal noted or to request a copy from the co-author: H. D. Riley, Jr., M.D., Professor of Pediatrics, University of Oklahoma Medical Center, Oklahoma City.

ECHINOCOCCOSIS—NEW YORK CITY

USDHEW PHS NCDC Wkly Rpt Morb & Mort 17(2): 20, Jan 13, 1968.

A case of echinococcosis has been reported in a 72-year-old Armenian woman, a resident of New York City. Her exposure to echinococcosis occurred 56 years prior to the onset of her illness, between 1907 and 1911 in Palestine, where she had tended sheep while a student in a convent school. The patient reported a history of good health until January 1967, when her present illness first became manifest. She was hospitalized, and upon examination, was found to have diabetes, glaucoma, congestive heart failure, abnormal liver function tests, and a large defect in the left lobe of the liver, demonstrated by liver scan. A carcinoma was diagnosed as the result of a needle biopsy of the defective area.

From Jan to Aug 1967, the patient was seen in several hospitals. On the third hospitalization, she underwent an exploratory laparotomy and cholecystectomy. Following hospitalization, while convalescing at a nursing home for 2 months, the patient complained of occasional abdominal pain. Increasing right upper quadrant pain necessitated a fourth hospitalization. A liver scan again showed a defect in the left lobe of the liver, and a selective coeliac artery angiogram showed a mass lesion in the right lobe of the liver. The hemagglutination inhibition and bentonite flocculation tests for echinococcosis were performed, and were strongly positive. The patient underwent surgery, at which time the secondarily infected echinococcus cysts were drained, but she died shortly after surgery from gastrointestinal hemorrhage and acute pulmonary edema.

Editor's Note: Because an echinococcosis cyst can persist for a prolonged or indefinite period of time before becoming symptomatic, a history of residence of a patient in an area endemic for echinococcosis, should cause consideration of the diagnosis of hydatid disease.

KNOW YOUR WORLD

Did You Know?

That a 20-year-old soldier has been given a permanent assignment to Fort Devens, Mass. as a personnel clerk because of his unique blood?

Dr. L. Molthan, Director of Temple University Hospital's blood bank in Philadelphia, explains that instead of being blood group "O" as the Army had thought, the soldier's blood was found to be so rare that he is stock-piling his own blood for freezing in case he ever needs a transfusion. He had an A-h type of Bombay blood found in only one person before—a Czechoslovakian nurse.[1]

That a synthetic juvenile hormone, a compound that effectively controls the yellow-fever mosquito, is also effective against *Pediculus humanus*, a kind of body louse that carries with it the threat of typhus epidemic?

Although typhus is rare today, there is always the possibility of its spread through poverty-ridden or war-torn parts of the world. It is reported from the Harvard School of Public Health that a synthetic juvenile hormone is lethal to both adult lice and to unhatched eggs. Eggs were tested on wool and nylon pads treated with the hormone and less than 25% survived. Controls tested on same kind of padding with peanut oil, hatched about 85% of the time. Exposure to the hormone in varying concentrations also kills adult lice and inhibits normal sexual development of nymphs. Findings were reported in the July 1967 Proceedings of the National Academy of Sciences, stated that lice have become immune to most insecticides.[2]

That British Ministry of Overseas Development has authorized a grant of $140,000 to build and equip a center near London for the study of insect carriers of tropical diseases.[3]

That the tsetse fly has been eradicated from about 2,000 square kilometers of Mozambican territory and about 4,000 more square kilometers are being cleared of this disease vector?

Under the direction of the Anti-Trypanosomiasis Mission, trypanosomiasis campaigns in Portugal, Rhodesia, and South Africa have utilized almost 20,000 liters of insecticide.[4]

That Weil's disease has been reported from Fukushima, Miyagi and Niigata as well as other northeastern provinces of Japan?

The incidence showed a decrease in the last few years, but the 1967 incidence exceeded previous totals. The mortality from Weil's disease has risen considerably in 1967. In the prefecture of Niigata, a total of 67 patients were reported during Aug-Oct 1967; 7 of these dead. The Government of Japan through its public health service has undertaken a survey of Weil's disease and all measures to stop the epidemic are in effect.[5]

That 33% of Mexico's population is affected by amoebic intestinal parasites?

According to a gastroenterologist of the Mexican Social Security Institute Hospital, amoebic parasites is the most extensive of parasitic diseases in Mexico, with 10% of the victims dying from the disease. Gravest complication is amoebic liver abscess.[6]

That an incidence rate of phenylketonuria in newborn infants in New York State was estimated in 1965 to be 15,000 and in 1966—13,000?

The prevalence of the clinical form of the disease in the total population of New York was 43,000 from data canvassed of State Schools of mental retardates, State mental hospitals, or by examination of relatives of persons known to have phenylketonuria.[7]

That on 15 January 1968, the 25th millionth West African received smallpox vaccine under the U.S. Government program?

The recipient was a 4-year-old girl from Asamoah—Ampofo, 30 miles northeast of Accra, Ghana, who received a certificate from the USPHS.[8]

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EDITOR'S SECTION

LAW AND MEDICINE

Francis A. Allen, LL.B., Univ Mich Med Cent J 33(4): 158–159, July-August 1967.

The relations of law and medicine have not always been serene. Indeed, in some areas, such as psychiatric medicine, they have sometimes been tempestuous. Nor should this occasion great surprise. Doctors and lawyers are among the most influential groups in our society. Both have achieved substantial privileges, prestige, and freedom of action. Any group with a strong sense of identity and tradition possesses its ritual; and in the case of doctors and lawyers this sometimes takes the form of mutual castigation. I for one am not as concerned about this phenomenon as some. It is possible that a certain tension between us is necessary to social well-being. In any event, the pleasures of verbal aggression being what they are, I do not anticipate that our discourse will speedily and totally lose its edge.

On the other hand, this tendency toward ritualistic acrimony can be overdone. There is genuine basis for concern when our differences arise from fundamental ignorance of the other's values and objectives. This is true because an increasing number of problems confronting mankind require for their solution the united efforts of both professional groups. I anticipate that the years ahead will see a marked tendency toward mutual understanding and cooperation. This, I believe, will occur, not because the next generations of doctors and lawyers will be more virtuous or altruistic than their fathers, but because the exigencies of the situations to be encountered will demand this movement toward rapprochement.

Probably no other profession is so much involved in the total life of the times as is the law. This is true because there is scarcely an issue involving man-in-society that is not in some manner or degree a concern of the law, and hence of lawyers. It follows that in the future, as in the past, the law will be deeply involved in the important and characteristic issues of the society. Today surely one of the facts of overwhelming importance for us all is that we are living through the most remarkable knowledge explosion in the history of mankind. Nor does there appear any indication that this rapid expansion of knowledge and technology will soon abate. These facts are of the greatest significance for the law. The new knowledge is creating a new world, and it is in this new world that the law must function.

The involvement of the law with new knowledge and technology is not unique to the twentieth century. The rise of the corporate form of business enterprise in the last century, for example, in large measure reflected the adaptation of the law to the new technology of the steam engine which was, in turn, related to advances in the science of thermodynamics. New knowledge gives rise to two characteristic types of problems or functions for the law. First, there are the problems of creating social and legal arrangements for the effective utilization of new knowledge so that it may make its contributions to human needs. If knowledge and technology are to be exploited to advance human welfare, resources must be accumulated and arrangements established to achieve this end. It is here that law and lawyers perform one of their most creative and vital functions.

But there is another aspect to the relations of law and new knowledge. Knowledge gained from studies, as Sir Francis Bacon observed in the course of one of his most profound observations, does not apply itself. And the journey of the new knowledge from laboratory, clinic, and library to the courts, legislature, and administrative agency may be one full of perils and unpleasant surprises. New knowledge may be embraced to advance insidious ends and become debased and adulterated by propaganda and special pleading. When the new knowl-

Dean of the Law School and Professor of Law, The University of Michigan, Ann Arbor.

edge is of the sort that may be employed in ways that profoundly affect human dignity and human volition, it is vital that the uses of new knowledge be tested against the basic political values of the community. Here again the law performs an indispensable function: that of insuring that the utilization of knowledge will nourish and maintain, rather than destroy or weaken, the fundamental human values.

What has already been said may be sufficient to indicate something of the importance of the relations of law and medicine in the future. It perhaps may also suggest an overriding identity of interests of the two professional groups. Medical science and the related disciplines constitute one of the primary sources of new knowledge in the modern world. Much of this knowledge and technique has enormous social impact. Already enlightened members of both professions have united in efforts to confront the critical needs for population control. It hardly requires emphasis that the quality of human life and hopes for a genuine international order in the years ahead depend upon the success of these efforts. Doctors and lawyers are advancing the cause of adequate abortion legislation. Control of narcotic addiction demands, in the first instance, greater attention by both groups and the combining of skills and insights in a common undertaking. There are many unsolved problems in the area of forensic medicine. Forbearance and good will are required of both professions. Lawyers must be sensitized to the indignities and inefficiencies of the trial process insofar as it involves expert testimony, particularly medical testimony. Doctors, on the other hand, must gain some sympathetic understanding of the adversary process and of the vital contributions it makes to the maintenance of a free society. Looking a little ahead we can see dimly the outlines of issues likely to be posed by the new genetics, issues presenting basic value choices and demanding the combined wisdom of the legal and scientific professions. The lengthening of the span of life following from medical advances raises questions concerning the quality of life for the aged, and this also will require increasing interdisciplinary efforts in the search for answers.

There are many other dimensions to the relations of law and medicine. One is illustrated by the community psychiatry movement. When psychiatry moves out of the private consulting rooms and seeks aggressively to expand the scope and range of its services in the community, it will inevitably encounter as never before the frustrations and limitations of community action. Both the psychiatric and legal professions are facing, and will continue to face, unfamiliar issues arising from the necessary effort to extend services to classes of the society that have not been the primary recipients of these services in the past. If I read the literature of community psychiatry correctly, therapists are discovering that assumptions derived from experience with middle-class patients are not always serviceable when treating the lower-class patient. New strategies and new techniques are, therefore, demanded. Comparable problems are being encountered by lawyers confronting the legal problems of the poor. Few legislators and judges are recruited from the lower orders of society, and it is being discovered that the middle-class stereotype that provides the assumptions for most law making is often inadequate for effective solution of the legal problems of these groups. The cultural factor is thus becoming an element of increasing significance to both professions. I do not know whether the experience of the two professions as they struggle with these problems will prove transferable. But I suspect that it will be discovered that they will often have to unite their efforts if the job is done satisfactorily. The problems of the problem family frequently include legal, emotional, and medical ingredients. A concentrated attack across the board will be required. Inevitably the effort will be interdisciplinary; and this, in turn, will require an awareness of the nature of the problem and a willingness on the part of all the professional groups involved—doctors, lawyers, and social workers—to launch a unified and coordinated effort.

All too often in the past doctors and lawyers have met primarily in an adversary posture. Cross-examination in court, abrasive disputes concerning procedures for the commitment of the mentally ill or the legal tests for the determination of criminal responsibility are typical of these confrontations. The issues involved in these encounters are real and their importance to the community cannot properly be minimized. They will not suddenly disappear. But these issues that have typically divided us are not the only problems of mutual concern, nor are they of greatest importance. We are on the threshold of a new range of problems that will tax to the limit our knowledge and ingenuity. Characteristically they will demand the insights and experience of many professional groups. How well we shall respond to these new challenges will depend

in no small part on the capacity of doctors and lawyers to work together in a common purpose.

XANTHINURIA

Xanthinuria is a very rare disorder characterized by deficient production of uric acid, a major end product of the metabolism of purines derived from dietary protein. Public Health Service scientists have shown that xanthinuria results from the absence of an enzyme, xanthine oxidase, that generates uric acid from hypoxanthine and xanthine, both intermediate compounds in purine metabolism.

In patients with xanthinuria, the metabolic block in uric acid production causes the accumulation of hypoxanthine and xanthine in the blood. The excess is excreted by the kidneys; but, because both compounds are only sparingly soluble in urine, they may crystalize out of solution to form kidney stones. This appears to be the only potentially serious consequence of the disorder. Stone formation can usually be avoided if the patient drinks plenty of water and avoids glandular meats and other high-purine foods.

There are only 7 or 8 known cases of xanthinuria in the world. One of these is presently a study patient at the Clinical Center of the National Institutes of Health.

The investigators found that the blood uric acid level in this patient was only 0.5 milligrams per 100 milliliters of plasma (normal range: 3.5–6 mg/100 ml). Her daily urinary excretion of uric acid was 6 mg., whereas the normal excretion rate is 250–600 mg. per day. These findings indicated that the patient was either destroying uric acid by some abnormal metabolic process or else was not producing it at a normal rate.

Subsequently the scientists devised new, extremely sensitive techniques to measure the activity of the enzyme xanthine oxidase in human tissues. The tissues of the patient with xanthinuria exhibited no detectable xanthine oxidase activity.

The studies have not only clarified the nature of the metabolic defect underlying xanthinuria, but may also have relevance in newer therapeutic approaches to a very common disorder of purine metabolism: gout. In gout, the problem is excessive uric acid production. The excessive blood levels of uric acid may result in deposition of uric acid crystals in the joints.

Earlier therapy to prevent recurrent attacks of gout involved the use of drugs to hold blood levels of uric acid down by increasing urinary excretion of uric acid. However, a new drug called allopurinol reduces blood uric acid levels by blocking its production from xanthine and hypoxanthine. It does so by inhibiting the enzyme xanthine oxidase.

Thus, while receiving allopurinol, these patients are made "xanthinuric." The resultant increase in blood levels and urinary excretion of hypoxanthine and xanthine raises the possibility of precipitation and kidney stone formation, although kidney stones have not yet been a reported side effect of allopurinol therapy.

In any event, the rare patient with xanthinuria provides a living model for gout patients receiving allopurinol on a long-term basis.

These findings were reported at the recent annual meeting of the American Association of Clinical Chemists by Dr. Karl Engelman, of the National Heart Institute's Experimental Therapeutics Branch.

Drs. Richard W. E. Watts, James R. Klinenberg, Albert Sjoerdsma, and J. Edwin Seegmiller participated in these studies with Dr. Engelman.—US DHEW, National Heart Institute, Bethesda, Md.

MITHRAMYCIN THERAPY

For the past two years the Naval Hospital, Chelsea has been permitted to use the experimental drug Mithramycin, an antineoplastic agent provided by Pfizer Company. Studies indicate that Mithramycin may be particularly effective in treating metastatic embryonal cell carcinoma of the testes.

During the course of the investigation, it was found that the bleeding time was a useful indicator of incipient drug toxicity. They are most anxious to study this phenomenon further. A reliable toxicity indicator would make the use of this potent drug safer and possibly extend future use to a wider variety of neoplastic conditions.

To continue these studies additional cases are needed. In support of this investigation, it is suggested that hospitals having or admitting in the future, Navy or Marine Corps patients with disseminated testicular embryonal cell carcinoma, discuss the cases with the Commanding Officer, Naval Hospital, Chelsea, Massachusetts.

It is believed that careful usage of the drug in these cases would offer the chance for a number of remissions and provide an excellent opportunity for further investigation of bleeding time abnormalities during Mithramycin therapy.—BuMed.

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